HOSPITAL LIBRARY

Vol. 31 OCTOBER, 1947 No. 4

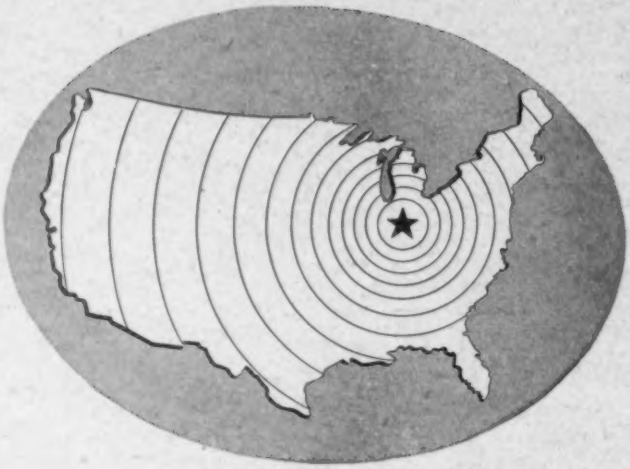
THE JOURNAL OF PEDIATRICS

A MONTHLY JOURNAL DEVOTED TO THE PROBLEMS AND DISEASES OF INFANCY AND CHILDHOOD

BORDEN S. VEEDER
St. Louis
Editor

Published by THE C. V. MOSBY COMPANY, 3207 Washington Blvd., St. Louis 3, U.S.A.
Copyright 1947 By The C. V. Mosby Company

Table of Contents on 3rd Cover



Pharmaceutical network

Lilly penicillin products are available to retail and hospital pharmacists from over two hundred service wholesalers located in every corner of the United States. No matter where you may be, Lilly penicillin products are near you. For quality and service, specify Penicillin, Lilly.

■

Penicillin

ELI LILLY AND COMPANY

INDIANAPOLIS 6, INDIANA, U.S.A.

Vol. 31, No. 4, October, 1947. The Journal of Pediatrics is published Monthly by The C. V. Mosby Company, 3207 Washington Blvd., St. Louis 3, Mo., Subscription price: United States, its possessions, Pan-American Countries, $8.50 a year; Canada, $10.00 (Canadian Currency); Foreign, $9.50. Entered as Second-Class Matter June 29, 1932, at the Post Office at St. Louis, Missouri, under the Act of March 3, 1879. Printed in the U. S. A.

The Journal of Pediatrics

VOL. 31 OCTOBER, 1947 No. 4

Original Communications

A NEW TREATMENT FOR DIAPER RASH

PRELIMINARY REPORT

REUEL A. BENSON, M.D., LAWRENCE B. SLOBODY, M.D., LOIS LILLICK, PH.D.,
ANTHONY MAFFIA, M.D., AND NORBERT SULLIVAN, M.D.
NEW YORK, N. Y.

DIAPER rash is the most common skin condition encountered in infants and young children. It is a dermatitis which is usually limited to the skin in contact with the wet diaper: the buttocks, thighs, genitalia, and lower abdomen. The lesions are characteristically erythematous or papulovesicular and may go on to ulceration. Ulceration of the external urinary meatus is particularly troublesome.

In 1921 Cooke[1] demonstrated classically that the ordinary diaper rash is an ammonia dermatitis. He has shown that "the cause of the NH_3 production is entirely due to bacterial decomposition of urinary urea into free ammonia, and the principal organism concerned is the *B. ammoniagenes*, a saprophytic gram-positive bacillus which originates in the feces and infests the skin of the diaper region. When the diaper is wet by urine, a good culture medium is furnished with a favorable T° for their growth, and abundant ammonia production follows. The strong odor as well as the skin irritation are commonly noted in the morning after the child has lain in a wet diaper for some hours."

It follows that "the prevention and treatment of ammonia dermatitis is dependent on preventing ammonia formation in the diaper by inhibiting bacterial growth and this is readily accomplished by the use of a nonvolatile antiseptic in the diaper itself." Cooke initiated the use of 1:4,000 bichloride of mercury as a final rinse for the diapers. Physicians for many years have found this antiseptic prevents bacterial growth and ammonia formation. With the elimination of the cause of the skin irritation, the eruption disappears rapidly. Bichloride of mercury is not an ideal antiseptic because of its well-known poisonous qualities. Gordon[2] hesitates to recommend it for this reason and because of the difficulty of insuring the correct concentration. The laity fear the

From the Departments of Pediatrics and Bacteriology, New York Medical College, Flower and Fifth Avenue Hospitals.

Aided by a grant from Homemakers' Products Corporation, New York, N. Y.

use of bichloride of mercury and complain of the corrosive action on gold rings. Boric acid has been used for the treatment of diaper rash. It is safe but has not been found efficacious by most observers.

We have been searching for a safe and efficient bactericide against *Bacillus ammoniagenes*. The results with one of the quarternary ammonium compounds, para di-isobutyl-cresoxy-ethoxy-ethyl di-methyl benzyl ammonium chloride monohydrate, warrant early report. This drug was supplied to us as Diapene.*

PLAN OF STUDY

The bactericidal action of Diapene was tested in vitro on *B. ammoniagenes*. Contact tests with concentrated solutions of the drug were made on our own skins and then on children, infants, and newborn infants. Children with diaper rash were treated by impregnating the diapers with Diapene.

RESULTS

The bactericidal effect of Diapene on *B. ammoniagenes* in vitro is found in Tables I and II. The cup-plate method indicates inhibition up to 1:110,000. The tube method, which is more accurate, shows the bactericidal action up to approximately 1:200,000. The drug performs slightly better at body temperature than room temperature.

TABLE I. EFFECT OF DIAPENE ON B. AMMONIAGENES

CUP-PLATE METHOD OF TESTING (EXTRACT AGAR MEDIUM)	
DILUTION OF DRUGS	INHIBITION ZONE (DIAMETER IN MM. BEYOND CUP)
1: 1,000	70
1: 10,000	40
1: 20,000	32
1: 30,000	31
1: 40,000	28
1: 50,000	24
1: 70,000	23
1: 80,000	23
1: 90,000	20
1:100,000	17
1:110,000	Very slight
1:120,000	No inhibition
1:130,000	No inhibition
1:140,000	No inhibition
1:150,000	No inhibition
1:200,000	No inhibition

*Amount of drug solution tested per cup, 0.2 c.c. Diameter of cup, 15 mm.

In Table III are the results of an experiment on the inhibition of ammonia formation. Two diapers were soaked in 1:10,000 dilution of Diapene, wrung out, and dried thoroughly. Two diapers were untreated. Sheets of heavy filter paper somewhat smaller in area than the diaper were soaked in filtered urine, placed on all diapers, and inoculated with 2 c.c. of a heavy suspension of organisms in urine. Diapers and filter papers were folded together and placed in a can to cut down evaporation (not airtight) and incubated at 37° C.

*Diapene is a product of Homemakers' Products Corporation.

TABLE II. EFFECT OF DIAPENE ON B. AMMONIAGENES

TUBE METHOD (EXTRACT BROTH MEDIUM)*		
DILUTION OF DRUG	BROTH CULTURE AT 37° C.	BROTH CULTURE AT ROOM TEMPERATURE
1: 50,000	No growth	No growth
1:100,000	No growth	No growth
1:110,000	No growth	No growth
1:120,000	No growth	No growth
1:130,000	No growth	No growth
1:140,000	No growth	No growth
1:150,000	No growth	No growth
1:160,000	No growth	No growth
1:180,000	No growth	No growth
1:200,000	No growth	Slight growth
1:500,000	No growth	Slight growth
Control	Heavy growth	Heavy growth

*Incubation at 37° C. and at room temperature for forty-eight hours.

TABLE III. AMMONIA FORMATION IN DIAPERS

	AFTER 15 HOURS	AFTER 20 HOURS
Two diapers treated with Diapene	No odor of NH_3	Odor of NH_3 not strong
Two untreated diapers	Strong NH_3 odor	Strong odor of NH_3

The diapers impregnated with Diapene did not develop an ammonia odor until after fifteen hours. By twenty hours the treated diapers had a faint odor of ammonia. The controls had a strong ammonia odor at fifteen and twenty hours.

The safety of Diapene on human skin was established by contact tests. First the powder was placed on our forearms and moistened. No irritant effects were noted. Then 180 children and infants and twenty newborn infants received patch tests soaked with a 1:5,000 solution. The patch was a 1″ square gauze which remained wet and in contact with the skin for twenty-four hours. No irritating effects on the skin were noted in any child, infant, or newborn infant. Of these infants and children, one hundred had the patch test repeated in ten days. There was no reaction.

Fifty infants with ammonia dermatitis have been treated with Diapene. The results are found in Table IV. The infants ranged in age from 1 month to 18 months of age. No mild cases were included in this series. Moderate rash denotes marked erythema or papulovesicular lesions. Severe rash indicates those which have gone on to ulceration.

The only treatment was impregnating the diaper with Diapene. The Diapene was supplied in the form of tablets. One tablet in 2 quarts of water provided an approximately 1:25,000 solution. Up to six washed diapers were placed in a basin and the solution poured over them. The diapers were permitted to soak for ten minutes, then wrung out and hung up to dry. These instructions should be followed to insure approximately equal concentrations in each diaper. Diapene is absorbed from solution by diapers almost quantitatively irrespective of the concentration of the solution. If diapers were introduced one at a time, all the Diapene might be absorbed on the first diaper placed in the solution.

The results in the fifty children were recorded after three and seven days of treated diapers. In three days thirty-one of the youngsters improved so that the ammonia dermatitis was definitely receding. In eighteen children the dermatitis could be considered cleared. In one, there was no response. After one week of treatment, forty-nine children were considered cleared; the one did not clear. Fourteen of the infants, after stopping the treatment, returned in two to four weeks with a mild ammonia dermatitis. Once more they responded immediately to the impregnated diapers. Nine of the mothers spontaneously said they no longer smelled ammonia in the diaper after treatment. Most of the others made the same statement, but only after direct questioning.

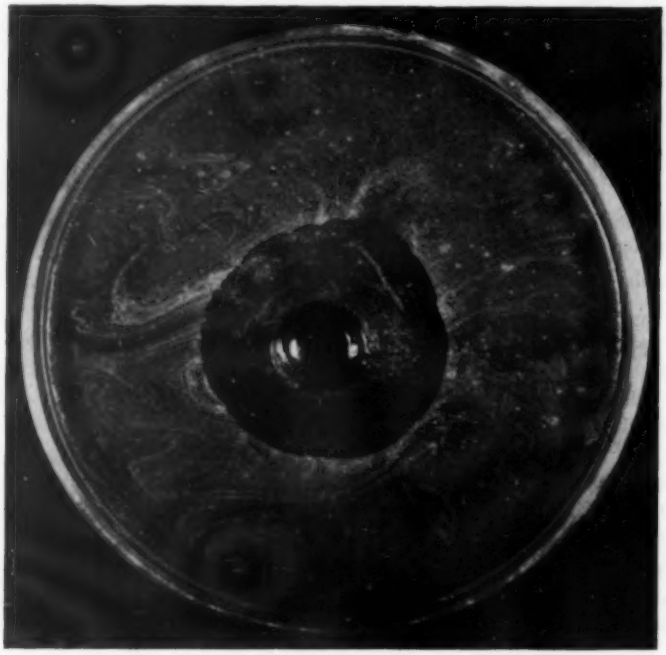


Fig. 1.—Dark area surrounding cup containing Diapene shows inhibition of the growth of the *B. ammoniagenes.*

COMMENT

In the past we have used bichloride of mercury or boric acid to impregnate the diapers of children with ammonia dermatitis. The value of the boric acid was slight and probably due to the more frequent changing of the infant's diapers. Mercuric chloride, 1:4,000 solution, has proved to be an effective antiseptic against *B. ammoniagenes.* A new bactericide should have equal or better efficacy and none of the disadvantages of mercuric chloride.

The marked bactericidal effect of Diapene on *B. ammoniagenes* in vitro has been confirmed clinically. It is our impression that Diapene has as much or more efficacy than mercuric chloride in ammonia dermatitis. Further-

TABLE IV. CHILDREN TREATED WITH DIAPENE

NAME	SEX	RACE	AGE (MO.)	SEVERITY OF RASH	RESULTS AFTER 3 DAYS	RESULTS AFTER 7 DAYS
1. V. S.	M	W	18	Moderate	Improved	Cleared
2. R. M.	F	W	6	Severe	Improved	Cleared
3. D. G.	F	W	12	Moderate	Improved	Cleared
4. S. R.	F	W	11	Severe	Cleared	Cleared
5. V. N.	F	W	3	Moderate	Improved	Cleared
6. C. R.	M	W	1	Moderate	Improved	Cleared
7. M. R.	F	W	12	Moderate	Improved	Cleared
8. C. W.	M	N	2	Moderate	Improved	Cleared
9. K. C.	F	W	2	Severe	Improved	Cleared
10. D. S.	M	W	1	Severe	Cleared	Cleared
11. C. H.	F	W	1	Severe	Cleared	Cleared
12. E. G.	F	W	4	Moderate	Cleared	Cleared
13. M. G.	F	W	4	Moderate	Cleared	Cleared
14. M. C.	F	W	10	Very severe	Cleared	Cleared
15. C. L.	M	N	2	Moderate	Improved	Cleared
16. C. L.	F	N	2	Moderate	Improved	Cleared
17. A. K.	M	W	3	Severe	Improved	Cleared
18. A. C.	M	W	1	Moderate	Improved	Cleared
19. F. S.	M	W	4	Moderate	Improved	Cleared
20. R. B.	M	N	4	Severe	Improved	Cleared
21. L. D.	M	W	7	Severe	Improved	Cleared
22. L. B.	F	W	1	Moderate	Improved	Cleared
23. J. K.	M	W	1	Moderate	Improved	Cleared
24. L. B.	M	N	6	Moderate	Improved	Cleared
25. V. P.	F	W	2	Moderate	Improved	Cleared
26. C. A.	F	W	5	Severe	Improved	Cleared
27. L. T.	F	N	6	Severe	Improved	Cleared
28. M. L.	M	W	4	Moderate	Cleared	Cleared
29. T. A.	M	W	7	Moderate	Cleared	Cleared
30. P. M.	F	W	5	Moderate	Cleared	Cleared
31. E. W.	F	W	22	Moderate	Cleared	Cleared
32. E. M.	F	W	9	Very severe	Cleared	Cleared
33. R. R.	M	W	26	Moderate	Not improved	Not improved
34. L. S.	F	W	8	Severe	Improved	Cleared
35. J. D.	M	W	2	Moderate	Cleared	Cleared
36. R. C.	F	W	4	Moderate	Improved	Cleared
37. C. C.	F	W	13	Moderate	Improved	Cleared
38. H. M.	F	W	18	Severe	Improved	Cleared
39. D. C.	M	N	4	Moderate	Cleared	Cleared
40. M. R.	M	W	10	Moderate	Improved	Cleared
41. L. S.	F	W	13	Moderate	Cleared	Cleared
42. J. S.	F	W	9	Moderate	Improved	Cleared
43. R. P.	M	W	4	Severe	Improved	Cleared
44. C. W.	M	N	8	Moderate	Cleared	Cleared
45. R. V.	M	W	1	Moderate	Cleared	Cleared
46. F. F.	F	W	6	Moderate	Improved	Cleared
47. H. A.	F	W	17	Moderate	Cleared	Cleared
48. F. M.	M	W	10	Moderate	Cleared	Cleared
49. R. D.	F	W	5	Moderate	Improved	Cleared
50. M. M.	M	W	4	Moderate	Improved	Cleared

more, if resistant rashes were encountered, the solution could be concentrated five times with no irritant effects on the skin.

In the treatment of ammonia dermatitis, all the diapers should be impregnated. In the prevention it is possible that only the night diapers would have to be treated. Usually the lying for long periods in the wet diaper loaded with NH_3 initiates the dermatitis. Our experiments (Table III) have shown that the Diapene-impregnated diaper will not develop an ammonia odor for at least fifteen hours.

SUMMARY

1. The efficacy of Diapene in ammonia dermatitis has been studied.

2. Diapene combines a high bactericidal effect against *B. ammoniagenes* with no irritation of the infant's skin.

3. Forty-nine infants with ammonia dermatitis were cleared within one week by impregnating their diapers with Diapene.

REFERENCES

1. a. Cooke, J. V.: Am. J. Dis. Child. **22**: 481, 1921.
b. Cooke, J. V.: Arch. Dermat. & Syph. **14**: 539, 1926.
c. Cooke, J. V.: Brennemann, Practice of Pediatrics **4**: Chapter 41, 1945.
2. Gordon, I.: Brit. M. J. **1**: 383, 1940.

THE SUBCUTANEOUS ADMINISTRATION OF SODIUM SULFADIAZINE

GILBERT B. FORBES, M.D., GEORGE DONNELL, M.D., AND JOHN C. HERWEG, M.D.
ST. LOUIS, MO.

THE subcutaneous route for parenterally administering the sulfonamide drugs, first introduced by Taplin,[1] has been used almost exclusively at the St. Louis Children's Hospital since early in 1942. During the succeeding years we have collected data with regard to the subcutaneous use of the various sulfonamides, which it seems desirable to publish, in view of the general preference for the intravenous route and the occasional comment in the literature that the subcutaneous route is unsatisfactory. This report compares the subcutaneous and intravenous methods of administering sodium sulfadiazine to infants and children, with special reference to its diffusion into the cerebrospinal fluid. Data on the parenteral use of sodium sulfapyrazine[2] and sodium sulfamerazine[3] are available in previous publications from this clinic.

METHODS

The solutions of sodium sulfadiazine for subcutaneous use were prepared by adding sterile powdered sodium sulfadiazine to sterile one-half fortified lactate-Ringer's solution* in amounts sufficient to make either a 1 per cent or a 5 per cent solution. Those for intravenous use were made up in 5 per cent concentration in distilled water. The solutions were prepared aseptically and were not subjected to further sterilization procedures before use. They were discarded if not used within twenty-four hours. The subcutaneous injections were made either in the axillae or thighs and the solution allowed to run in by gravity as rapidly as possible without producing undue tissue distension. The intravenous injections were made in a scalp or antecubital vein at a fairly rapid rate, the time consumed in the largest single injection (100 c.c. in a 22.7 kg. subject) not exceeding ten minutes.

The patients employed for this study exhibited no evidence of renal or enteric disease. Samples of whole blood for sulfadiazine analysis were obtained from puncture of the toe or finger, those of plasma from oxalated venous blood. Lumbar punctures were done under local metycaine† anesthesia. Analyses were made for only the "free" form of the drug, and all figures given herein refer to this form. Chemical analyses were made by the method of Bratton and Marshall[4] adapted for a sample of 0.1 c.c. The readings were made on an Evelyn photoelectric colorimeter and compared to a standard curve made, and periodically checked, in this laboratory.

From the Department of Pediatrics, Washington University School of Medicine, and the St. Louis Children's Hospital.

A portion of the sodium sulfadiazine used in this study was kindly furnished by the Medical Research Division of Sharp & Dohme, Inc.

*A mixture of three parts ⅙ molar sodium lactate with four parts Ringer's solution. The pH of this solution, as prepared at the St. Louis Children's Hospital, is slightly above 7.0.

†Benzoyl-gamma-2-methyl piperidino propanol hydrochloride.

EXPERIMENTAL STUDIES

Limitations of the Oral Route for Sulfadiazine Administration.—In order to determine the ability of the infantile gastrointestinal tract to absorb sulfadiazine, single doses several times as large as those routinely employed were given by mouth to a group of infants and the blood levels followed closely for the next eight hours (Fig. 1). The subjects were convalescing from infectious diseases or from surgical procedures; none was acutely ill at the time of the experiment. In only one of the infants, a 2-year-old child, did the blood level exceed 12.5 mg. per cent; in two of them (subjects 3 and 4) it approximated the levels usually noted with the standard initial therapeutic dose of 0.1 Gm. per kilogram body weight.

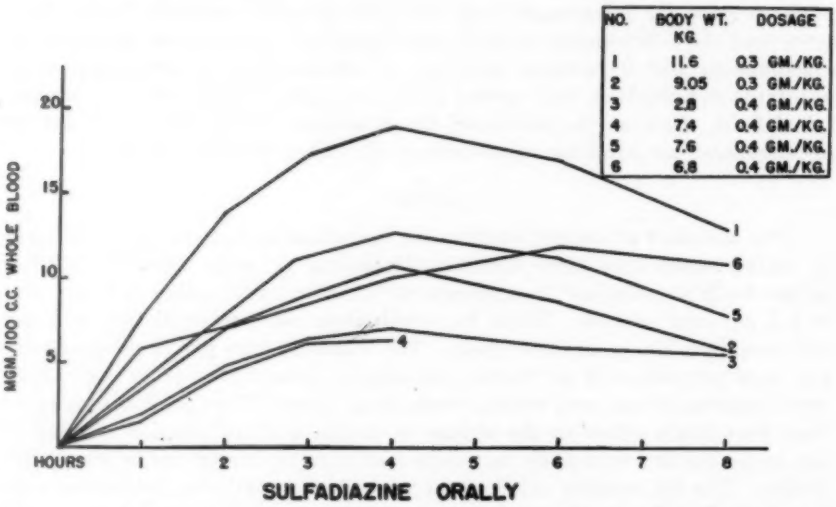


Fig. 1.—Whole blood concentrations of sulfadiazine following single large doses of sulfadiazine in infants.

A high blood level, already present by virtue of parenteral administration, cannot be maintained by oral administration in the majority of young children. Fig. 2 is representative of the course of the blood sulfadiazine level in the infant when parenteral therapy is stopped; even huge oral doses (0.8 Gm. per kilogram body weight per day) failed to prevent an immediate drop in the blood level when the subcutaneous route was abandoned.

It is evident that there are certain limitations, at least in young children, to the oral use of sulfadiazine in the usual form.

Results of Single Subcutaneous Dose of Sodium Sulfadiazine.—The subjects for these experiments were infants or young children with acute infections of various types, the subcutaneous dose of sulfadiazine being given as the initial part of their chemotherapeutic regime. Fig. 3 illustrates the whole blood concentration produced by varying amounts of sodium sulfadiazine administered

in 1 per cent solution to eight different subjects.* While doses of 0.1 and 0.05 Gm. per kilogram body weight do not result in unusually high levels, a dose of 0.3 Gm. per kilogram regularly effects a rapid rise in the blood concentration. In each of the five subjects in this latter group the blood level was 10 mg. per cent or above at the end of an hour, and in four of the five it exceeded 20 mg. per cent within two hours of the start of the subcutaneous infusion.

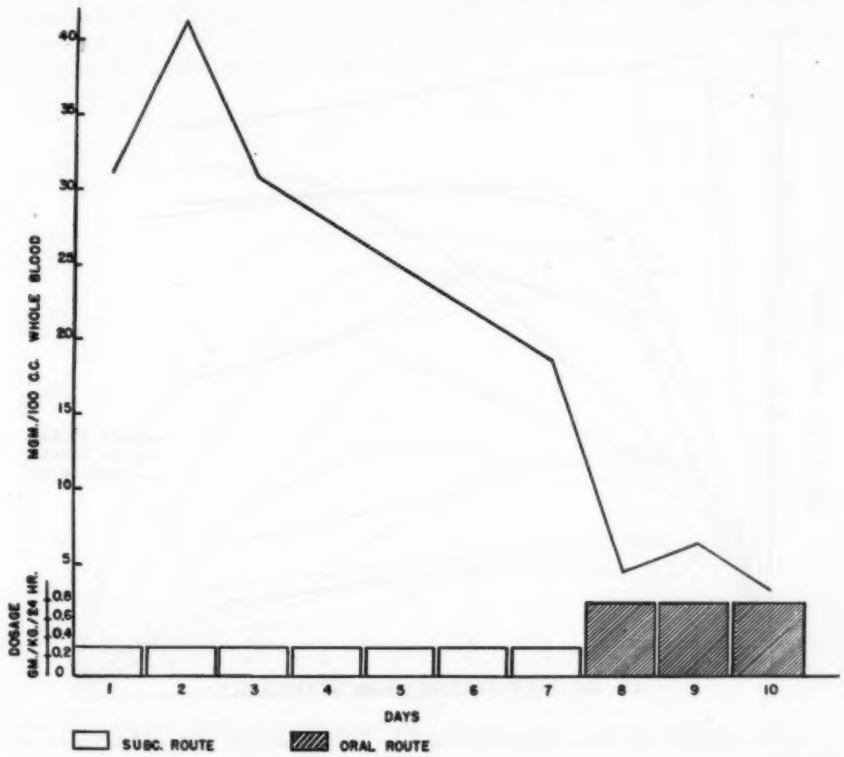


Fig. 2.—Whole blood concentrations of sulfadiazine with sustained high oral dosage in an infant whose blood level was originally raised to a high value through the subcutaneous administration of sodium sulfadiazine.

In one subject, who was dehydrated at the time of the infusion, absorption was extremely rapid, the blood level reaching 18.2 mg. per cent within thirty minutes and 39 mg. per cent in one hour.

In Fig. 4, data obtained by giving single 5 Gm. doses of sodium sulfadiazine subcutaneously to a group of children and adults are presented. Except for subject 6, in whom absorption was poor, this dose produced a satisfactory high level in those subjects 25 kg. or less in weight. In heavier individuals it does

*In these and subsequent charts, zero time refers to the time at which the subcutaneous infusion was begun.

not appear to be any more effective than does a comparable amount given by mouth. When the doses are calculated on the basis of body weight for the adults (subjects 8, 9, and 10), they are found to range between 0.04 and 0.09 Gm. per kilogram. In comparison with similar amounts given to children, as illustrated in Fig. 3, the absorption in adults is seen to be considerably slower, for the blood level is still rising at the end of eight hours, whereas in the children the peak of absorption appears at two hours.

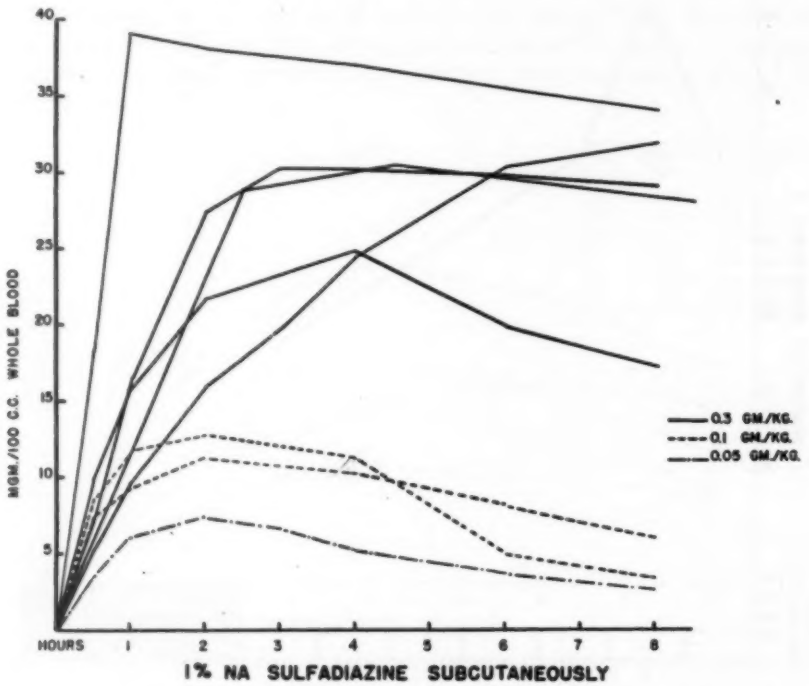


Fig. 3.—Whole blood concentrations of sulfadiazine following single subcutaneous doses of varying amounts of sodium sulfadiazine in 1 per cent solution to a group of infants and children.

Fig. 5 illustrates the course of the blood level following a dose of 10 Gm. administrated subcutaneously as a 1 per cent solution to three adults, this dose corresponding to 0.13 to 0.17 Gm. per kilogram body weight. Somewhat higher blood levels resulted, but here, too, absorption seemed to be definitely slower than in the case of the children.

The results of the subcutaneous administration of varying amounts of a 5 per cent solution of sodium sulfadiazine to a group of three young children are presented in Fig. 6. With the use of large doses, absorption seems to be a little more rapid than with the 1 per cent solution, while with doses of 0.1 Gm. per kilogram the two solutions are similarly absorbed. Accurate comparison can hardly be made, however, from the data at hand.

Diffusion of Sulfadiazine into the Cerebrospinal Fluid. —A study was made of the rapidity with which sulfadiazine enters the cerebrospinal fluid from the blood, with the idea in mind of comparing the intravenous and subcutaneous routes of administration. The subjects employed for this portion of the study were all suffering from pyogenic or tuberculous meningitis or meningoencephalitis at the time of the experiments. Samples of lumbar spinal fluid and of venous blood were obtained at regular intervals following the administration of sodium sulfadiazine. Plasma, rather than whole blood, analyses were run on these subjects, for it is the plasma sulfonamide concentration which controls the level in the extracellular fluid.

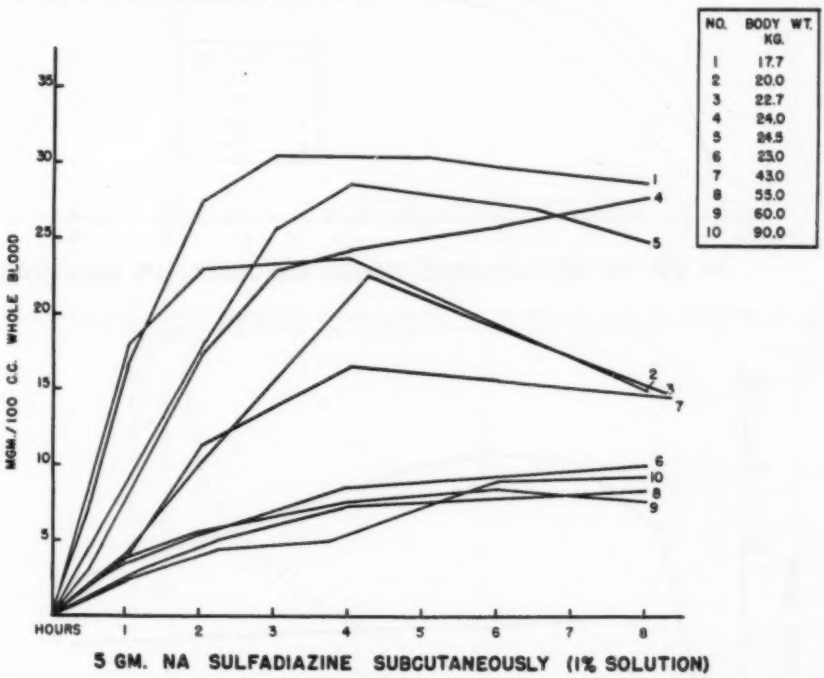


Fig. 4.—Whole blood concentrations of sulfadiazine following a single 5 Gm. dose given subcutaneously as a 1 per cent solution to a group of adults and children.

Two patients with chronic meningeal infection were given identical amounts of sodium sulfadiazine by the two routes on separate days. In Fig. 7 the results of giving a patient with meningoencephalitis 0.1 Gm. per kilogram of body weight by the intravenous and subcutaneous routes are illustrated. Despite the wide discrepency in plasma concentrations immediately following the injections (71.5 versus less than 1 mg. per cent), the concentrations at eight hours are almost identical. In sharp contrast, the spinal fluid concentrations do not differ greatly from each other at any time throughout the period covered by the experiment.

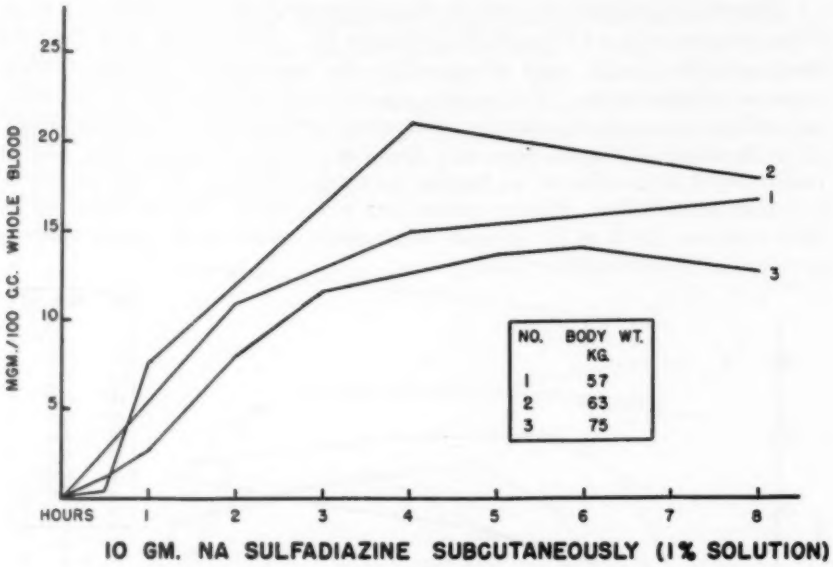


Fig. 5.—Whole blood concentrations of sulfadiazine following a single 10 Gm. dose given subcutaneously as a 1 per cent solution to a group of adults.

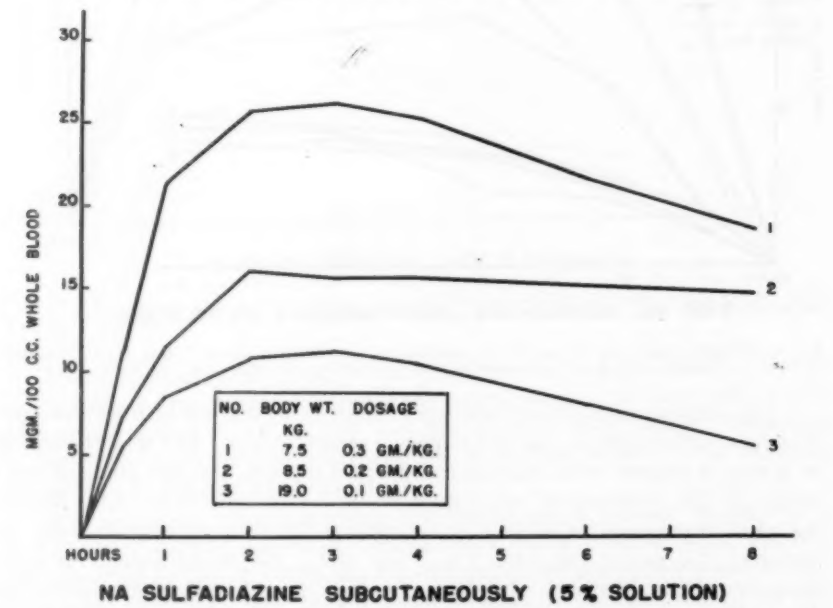


Fig. 6.—Whole blood concentrations of sulfadiazine following the subcutaneous administration of varying amounts of a 5 per cent solution of sodium sulfadiazine to a group of infants.

The second patient, an infant with tuberculous meningitis, was subjected to three such experiments in which two solution strengths, 1 and 5 per cent, were used subcutaneously and compared to an intravenous injection (Fig. 8).

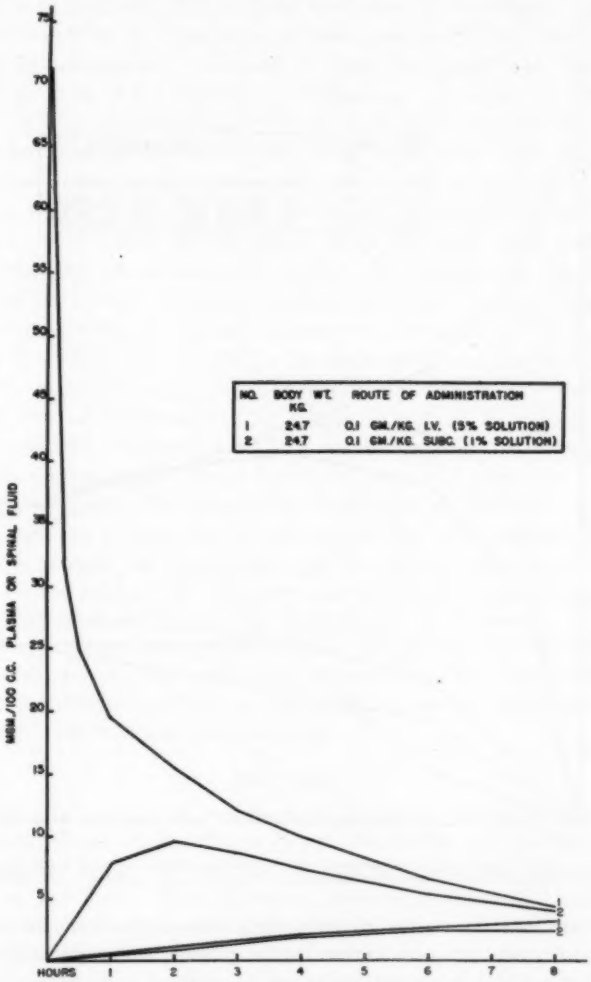


Fig. 7.—Plasma and spinal fluid concentrations of sulfadiazine following identical per kilogram single doses administered intravenously and subcutaneously to the same patient on different days.

The intravenous route produced slightly higher spinal fluid concentrations of sulfadiazine throughout the entire eight hours; however, the use of a 5 per cent solution subcutaneously appeared to possess no consistent advantage over the more commonly employed 1 per cent solution. These data and those of Fig.

7 illustrate nicely the constancy of the equilibrium concentration of sulfadiazine in the blood attained in six to eight hours, which is independent of the mode of administration of the drug.

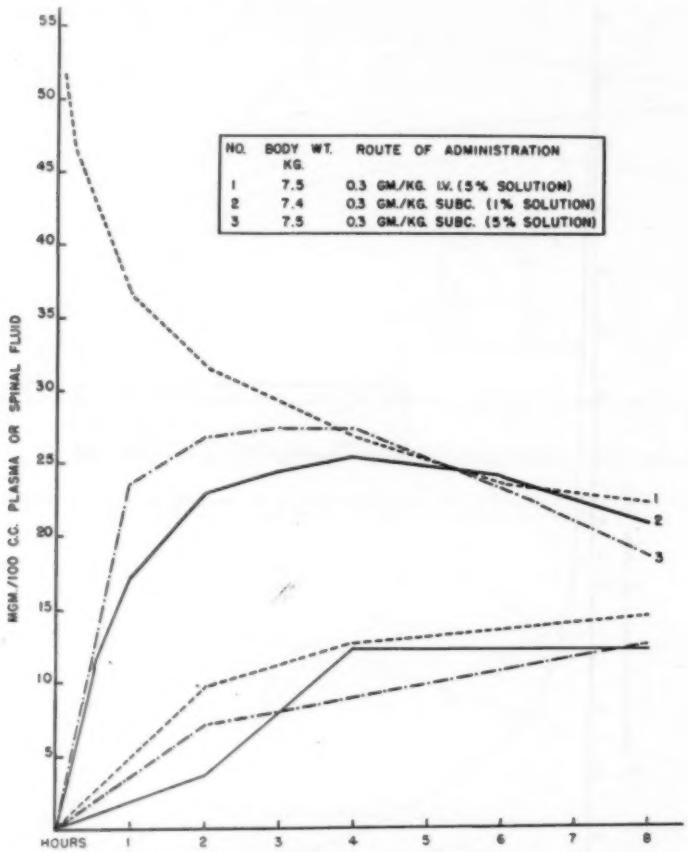


Fig. 8.—Plasma and spinal fluid concentrations following identical per kilogram single doses administered intravenously and subcutaneously to the same patient on different days.

All of our data in regard to accurately timed simultaneous observations on the concentrations of sulfadiazine in the plasma and cerebrospinal fluid of patients receiving single parenteral doses of sodium sulfadiazine, either subcutaneously or intravenously, are plotted in Fig. 9*A*, and 9*B*. In these figures the observations at two, four, and eight hours subsequent to the injection of the sodium sulfadiazine solution are indicated by small and large dots or circles, the plasma concentrations on the ordinates being plotted against the spinal fluid concentrations on the abscissae. Equations were calculated to represent each series of plotted points by the method of least squares, and these equations together with the curves they represent are shown in each figure. Admittedly,

in some respects more data should be at hand in order to permit such calculations; nevertheless, the general trend is clearly evident. Equilibrium has evidently been established by the time eight hours have elapsed, for the points fit in nicely with a straight line passing very close to the origin. The data for the two and four hour observations, however, are better represented by parabolic curves, indicating that sulfadiazine enters the spinal fluid somewhat more rapidly at high than at low plasma concentrations. A definite lag in the establishment of blood-spinal fluid equilibrium is evident, for the curves for the successive time observations incline more and more away from the y-axis. It is further evident that for a given attained plasma concentration the spinal fluid level is higher following intravenous administration. This latter point is brought out more clearly in Fig. 10, in which the spinal fluid concentrations, calculated from the equations given in Fig. 9*A* and 9*B*, are plotted for the three observation periods at three different arbitrary plasma levels. At the end of two hours, with an attained plasma concentration of 10 mg. per cent, intravenous administration results on the average in a spinal fluid concentration of 2.0 mg. per cent as against 1.0 mg. per cent for the subcutaneous route. Similarly, a dose of intravenously administered sodium sulfadiazine sufficient to produce a plasma concentration of 20 mg. per cent at two hours results in a spinal fluid concentration almost indentical with that produced by a plasma level of 30 mg. per cent after subcutaneous injection of the drug. The time lag for the subcutaneous as compared to the intravenous route appears to be about two hours. It should be emphasized that in all of these studies time was measured from the start of the injection and not from its completion, for in so doing, it was felt that the therapeutic implications of the study could be better evaluated from a clinical standpoint. Since the majority of the subcutaneous infusions required from thirty to sixty minutes for their completion, the advantages of the intravenous route would have been less apparent had we chosen the latter point from which to plot our data.

DISCUSSION

It is evidently possible in infants and children to establish rather quickly and to maintain blood concentrations of sulfadiazine of any desired magnitude in the therapeutic range by means of the subcutaneous administration of the sodium salt of the drug. The difference between children and adults in the ability of their subcutaneous tissues to absorb sodium sulfadiazine is difficult to explain. The reason cannot lie in greater solution volumes, for absorption was definitely more rapid in the children receiving doses similar to those given to adults (Fig. 4). In fact, the reverse would be expected because of the larger subcutaneous tissue volumes available in adults.

During the four-year period in which we have routinely employed the subcutaneous route for the parenteral administration of the various sulfonamide drugs, it has proved satisfactory for the vast majority of patients. Subcutaneous administration has given satisfactory blood levels in edematous patients, unless edema is very marked, and in those in peripheral circulatory collapse.

It has been our practice to utilize this route for any patient in whom it is desired to establish quickly and thereafter maintain high blood sulfonamide concentrations, for those who are comatose or who vomit excessively, and for the young infant who is severely toxemic on admission to the hospital. Solutions of sodium sulfadiazine in 0.5 and 1.0 per cent strength are well tolerated by the

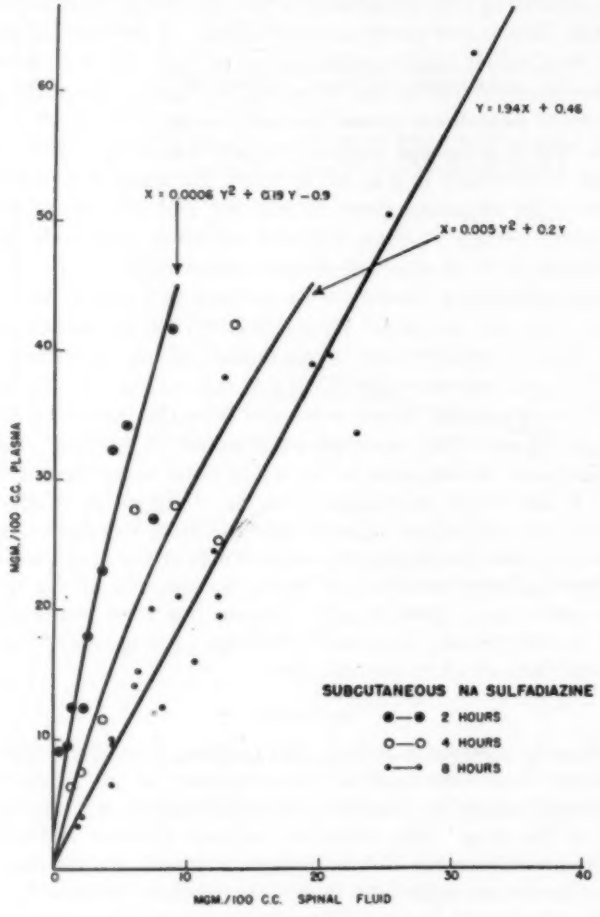


Fig. 9A.

Fig. 9.—The plasma-spinal fluid distribution of sulfadiazine in a group of infants and children with meningeal infection at various times after the administration of sodium sulfadiazine *A.*, subcutaneously, and *B.*, intravenously. (*For Fig. 9B, see opposite page.*)

subcutaneous tissues, and pain is no greater than that accompanying other subcutaneous infusions. Our experience with solution strengths greater than 1 per cent has been quite limited, but it has been reported that 5 per cent solutions do not provoke untoward reactions.[7] The calcium salt of sulfadiazine appears

to possess no advantage over the sodium salt.[8] We have preferred the subcutaneous to the intravenous route for parenteral sulfonamide therapy for the following reasons:

First, it is easier to administer solutions subcutaneously, particularly to small infants. Continuous or intermittent intravenous infusions are quite difficult to maintain over long periods, especially when many of the patient's available veins must be utilized for the purposes of parenteral feeding and other supportive measures. Using the subcutaneous route, it has been possible on many occasions to keep the sulfonamide concentration constantly at a level of 20 to 30 mg. per cent for as long as two weeks with a minimum of effort on the part of the resident house staff.

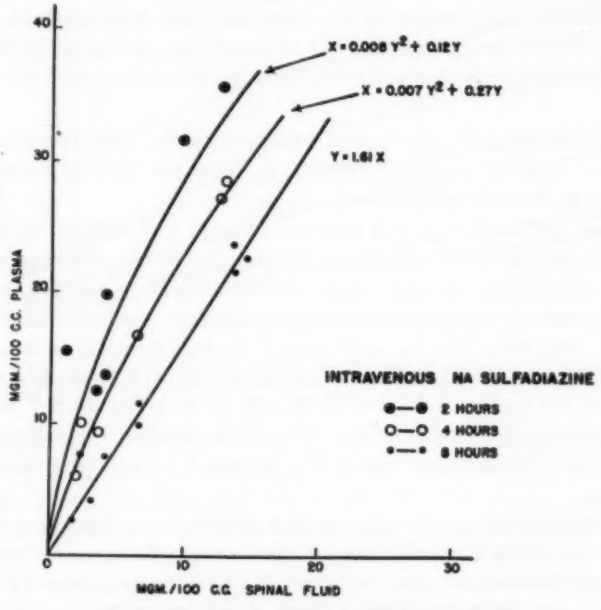


Fig. 9B.—*(For legend, see opposite page.)*

Second, an adequate amount of fluid and of alkali can be administered simultaneously with the sulfonamide drug. By using 0.5 per cent solutions, 200 c.c. of water are given with each gram of sulfonamide. Alkali in the form of 1/6 molar sodium lactate can easily be incorporated into the solution in sufficient quantities to render the urine alkaline. Thus three objectives are accomplished by one maneuver: chemotherapy, hydration, and alkalinization of the urine. If the intravenous route is used, the latter two of these objectives must be met by separate injections. It is for this reason that solution concentrations greater than 1 per cent possess no advantage in subcutaneous therapy.

Third, the initial, and unnecessarily high, spike in the blood sulfonamide concentration which follows intravenous injection is avoided. After subcutaneous injection the blood level rises to the desired value rather than falling to it as is the case with an intravenous injection. With comparable dosage, the attained blood level at the end of six to eight hours is similar with the two methods of administration. Many patients requiring parenteral chemotherapy are dehydrated on admission to the hospital and, therefore, should receive an intravenous injection of glucose or some other fluid in order to augment blood volume and promote diuresis prior to intravenous chemotherapy with its attendant high blood levels. In a chemotherapeutic sense, this maneuver wastes valuable time. These difficulties inherent in the intravenous method could no doubt be avoided by administering the drug solution as a continous intravenous drip, yet from a consideration of the technical difficulties involved in the setting up and proper maintenance of the necessary apparatus, at least in infants and young children, this method would offer no advantage over the subcutaneous route.

After witnessing two instances of osteomyelitis incurred at another hospital from the use of tibial marrow infusions, we have also been reluctant to adopt that method of fluid administration.

Although we have preferred to use a mixture of 1/6 molar sodium lactate and Ringer's solution as a vehicle for the subcutaneously administered solution of sodium sulfadiazine, isotonic saline or plain Ringer's solution may be used for this purpose. It is best to avoid the admixture of glucose as it may react chemically with sulfadiazine, particularly if the solution is heated. Since sodium sulfadiazine is unstable in boiling water, it is desirable to purchase either the sterile sodium sulfadiazine powder or a sterile 10 per cent solution from the manufacturer rather than attempt to sterilize the solutions as they are prepared. The solutions should be discarded if not used within twenty-four hours.

When sodium-lactate is used as the vehicle, one further precaution is necessary. To avoid the possibility of the undesirable presence of free lactic acid, one must be certain that the solution pH is greater than 6.5, preferably above 7.0, before adding sodium sulfadiazine. At a pH of below about 6.5 there will be enough free lactic acid to convert sodium-sulfadiazine into the free form which has a solubility of only 12.3 mg. per 100 c.c. Precipitation will then occur and render the solution worthless. For a similar reason sodium-sulfadiazine solutions should not be mixed with Amigen, which contains free amino acid. This problem has arisen because of the objectionable practice of some commercial firms in preparing sodium lactate solutions at an acid pH; it may be overcome by adjusting the pH with concentrated sodium hydroxide, using phenol red as an indicator, before the admixture of sodium sulfadiazine.

While there is a definite lag in the establishment of spinal fluid concentrations of sulfadiazine with the subcutaneous route of administration, as compared to the intravenous, the magnitude of this lag would not necessarily preclude

subcutaneous therapy in clinical practice except under the most unusual circumstances. The use of larger per kilogram dosages for the initial stages of therapy, however, tends to overcome this discrepancy. When the two routes are compared in the same patient, there is little difference between them (Figs. 7 and 8), though average values obtained from a series of patients indicate that the intravenous route produces a given spinal fluid level approximately two hours in advance of the subcutaneous.

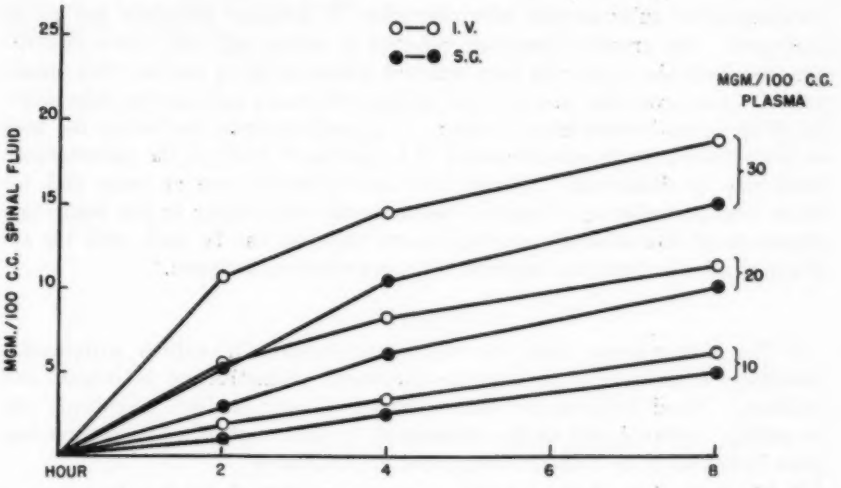


Fig. 10.—The spinal fluid concentration of sulfadiazine calculated from the data of Fig. 9 to occur for given attained plasma concentrations at various time intervals after the administration of sodium sulfadiazine intravenously and subcutaneously.

For the treatment of mild infections, the initial subcutaneous dose can be identical with that commonly employed for oral medication; namely, 0.1 Gm. per kilogram of body weight, with a maximum of 4 Gm. for the older children. When continued oral therapy is impracticable, we have found doses of 0.1 Gm. per kilogram repeated at eight to twelve-hour intervals sufficient to keep the blood level in the neighborhood of 10 mg. per cent. In those children with unusually severe infections, for whom blood levels of 20 to 30 mg. per cent are desirable, an initial dose of 0.3 Gm. per kilogram (maximum 8 to 10 Gm.) should be employed. From a large clinical experience, of which Fig. 2 is an example, we have found that sustained doses of from 0.3 to 0.6 Gm. per kilogram per twenty-four hours, given in divided doses at eight-hour intervals, are essential to the continuance of such levels. With such intensive therapy, however, because of possible variations in the attained blood levels, blood sulfadiazine analyses should be performed daily and dosage individualized. It is rather clear that oral administration fails to approach this goal in infants and children, although levels as high as 50 mg. per cent have been reported in adults.[5] Reinhold and his associates have noted that microcrystalline preparations of sulfadiazine are absorbed somewhat more rapidly by adults than is

ordinary sulfadiazine.[6] From the reported difference in attained serum levels, however, it would not appear that levels of the magnitude indicated above could be easily reached through the oral use of the microcrystals. In treating critically ill patients, moreover, high blood levels should be attained quickly, and although continued large oral doses would undoubtedly result in time in high blood levels, this accomplishment would involve undue therapeutic delay.

Though the subcutaneous administration of dilute solutions is quite satisfactory for the great majority of clinical cases, there may be instances in which intravenous or subcutaneous administration of stronger solutions are to be preferred: the grossly edematous subjects in whom salt and water restriction are desirable, those who have suffered extensive burns leaving little subcutaneous tissue available, and the rare patient who has a fulminating infection—the Waterhouse-Friderichsen syndrome is a good example—for whom the hour or two required for the establishment of a high blood level via the subcutaneous route may be disastrous. Further, for those patients seen at home and for whom transportation to a hospital would involve some delay in the institution of parenteral chemotherapy, an intravenous injection can be made with the aid of less apparatus than that required for a subcutaneous infusion.

SUMMARY

1. The subcutaneous route for the administration of sodium sulfadiazine constitutes a satisfactory method for parenteral chemotherapy in infants and children. Blood sulfadiazine concentrations of any desired magnitude can be quickly achieved and easily maintained by this method. The intravenous route is indicated only under exceptional circumstances.

2. The limitations of the infantile gastrointestinal tract for the absorption of sulfadiazine requires that the drug be administered parenterally on many occasions.

3. Adult patients do not absorb sodium sulfadiazine from the subcutaneous tissues as readily as do infants and children.

4. The rate of diffusion of sulfadiazine from the plasma to the cerebrospinal fluid in patients with meningeal infection is somewhat slower following subcutaneous administration in comparison to the intravenous method. This lag is not of sufficient magnitude, however, to contraindicate the subcutaneous route for the great majority of patients with bacterial meningitis.

5. In addition to adequate chemotherapy, hydration of the patient and alkalinization of the urine may be accomplished concurrently via the subcutaneous route by proper adjustment of the volume of the solution and its content of sodium lactate.

The kindness of Dr. Richard Maxwell, on whose service at the St. Louis City Hospital some of our studies were made, is gratefully acknowledged.

REFERENCES

1. (a) Taplin, G. V., Jacox, R. F., and Howland, J. W.: J. A. M. A. 114: 1733, 1940.
(b) Taplin, G. V., Custer, E. A., and Young, L. E.: J. A. M. A. 121: 313, 1943.
2. Barnett, H. L., Perley, A. M., Forbes, G. B., and Goldring, D.: Am. J. M. Sc. 206: 599, 1943.

3. Forbes, G. B., Perley, A. M., and Dehlinger, J.: J. PEDIAT. 28: 24, 1946.
4. Bratton, A. C., and Marshall, E. K., Jr.: J. Biol. Chem. 128: 537, 1939.
5. Plummer, N.: New York State J. Med. 43: 425, 1943.
6. Reinhold, J. G., Phillips, F. J., and Flippin, H. F.: Am. J. M. Sc. 210: 141, 1945.
7. Jorgensen, G. M., and Greeley, D. M.: J PEDIAT. 21: 325, 1942.
8. Nelson, C. T., and Spink, W. W.: Am. J. M. Sc. 206: 315, 1943.
9. Clarke, G. H.: Am. J. Dis. Child. 73: 565, 1947.

ADDENDUM

Since this paper was submitted for publication, an article has appeared by Clarke[9] in which a comparison is made between the oral and parenteral routes of sulfonamide administration in children.

RHEUMATIC FEVER RECURRENCES IN CHILDREN WITHOUT SULFONAMIDE PROPHYLAXIS: AN EVALUATION OF ENVIRONMENTAL FACTORS

ROBERT L. JACKSON, M.D., HELEN G. KELLY, M.S., CECILIA HEALY ROHRET, M.A., AND JULIA M. DUANE, M.D.
IOWA CITY, IOWA

INTRODUCTION

RENEWED interest has been focused on the recurrence rate of rheumatic fever since the introduction of chemotherapeutic agents for prophylaxis. This study was undertaken to determine the recurrence rate of a group of rheumatic subjects who have received special attention to improve their diets and level of environmental care, but who have not received sulfonamide drugs to prevent intercurrent infections. From this study we hoped to evaluate the relation of environmental factors to the course of the disease and to learn whether a high level of general care is sufficient to protect the children from recurrences, or if some children also should receive chemotherapeutic agents for prophylaxis.

SUBJECTS

Many of the children with rheumatic fever living in Iowa come under the care and supervision of the University Hospital and the State Services for Crippled Children's mobile clinics held throughout the state. In this study of the recrudescence of rheumatic fever, 266 of these children were included because they met the requirements of having an established diagnosis of rheumatic fever, were instructed in the therapy prescribed by the University clinic, and were under observation and supervision of the clinic for some time after the disease had become inactive. Only cases which could definitely meet the diagnostic criteria of Jones[1] were included in the study. A large group of children with questionable diagnoses were eliminated. The criteria of Taran[2] were followed to establish that the disease had become inactive. In general, the criteria used for the diagnosis of the disease also were used for determining a recurrence. Because of the marked variability in manifestations and for comparative purposes, the recurrences were classified as major, minor, or possible recrudescences according to the description of Hansen.[3] Very vague joint pains of short duration without any other symptoms, signs, or laboratory findings were not included as recurrences.

The calendar years in which the onset of rheumatic fever occurred for these children ranged from 1930 to 1946. The median year of onset is 1941. For 90 per cent, onset of the disease occurred during the period from 1935 to 1944, inclusive. Of the 266 patients, 208 (78 per cent) were in the active

From the Department of Pediatrics, and State Services for Crippled Children, State University of Iowa.
Aided by a grant from the American Medical Association.

phase of their disease when they were first placed under our care; in 9 per cent the disease had been inactive less than six months; in 4 per cent the disease had been inactive six months to one year; in 2 per cent the disease had been inactive one year to two years; and in 6 per cent the disease had been inactive more than two years. For two patients the disease had been inactive when they were first observed but how long it had been inactive was indefinite.

Sixty-one per cent of the children came under observation having had one attack or during the first attack; 25 per cent having had two attacks or during the second attack; and 14 per cent having had more than two attacks.

The median number of years of observation is 3.3; 27.4 per cent were observed five or more years and 23 per cent were observed less than two years. One hundred ninety-five (73 per cent) were under close medical supervision, that is, they made regular visits to our clinic. Seventy-one (27 per cent) were under indirect supervision, that is, they made an occasional visit to the clinic, and were followed by their local physicians and a public health nurse, who reported the condition of the children to us.

MANAGEMENT

As soon as a child with rheumatic fever comes under the supervision of the University Hospital or the mobile clinics of the State Services for Crippled Children, an investigation of the child's home environment is made by a trained medical social worker, and every effort is made to insure the child a good level of environmental care. If the child has active rheumatic fever, he is hospitalized or given sanatorial care, unless a high level of home care can be provided or the family refuses to accept institutional care. About half the children of the study group were hospitalized in the University Hospital. About a third received sanatorial care in the sanatorium connected with the Hospital. The remaining children were cared for in their own homes or in local hospitals during the acute phase of the disease.

The family of each child was instructed by the doctor and nurse and often by a dietitian regarding the importance of an adequate diet which should include the daily consumption of: one quart of milk; one or two eggs; one serving of meat, fish, chicken, or liver; two vegetables (½ cup is considered a medium serving); one orange, apple, or tomato; one other fruit in addition; one teaspoonful of cod liver oil; six teaspoonfuls of butter or margarine. They were also told that other foods such as bread, cereal, and potatoes could be added to satisfy the appetite and maintain correct weight, but under no circumstances were they to replace any of the above; cereal was not to be served more than once daily. Rather, the child was to be encouraged to eat larger quantities of fruits and vegetables; varieties of these were to be used so the child would not form likes and dislikes.

Each family was advised to have the child sleep in a room of his own whenever possible or at least to sleep alone, and to have about ten hours of rest each night. The importance of proper clothing was stressed, as well as control of temperature and humidity of the home. With regard to the care of intercurrent infection, the family was advised to have the child go to bed if

there were any sign of infection, and to consult the family physician as early as possible. If another member of the family had a cold, sore throat, or any other infectious disease, the child was to be kept away from that person, and the family physician notified. The family was told to have the child play with other children in the normal way, but to plan his activities to avoid fatigue. In addition, psychologic advice was given to prevent overprotection. The importance of persevering with a high level of care day after day and year after year was emphasized and re-emphasized at each clinic visit.

A detailed medical report regarding the child's condition and home management was sent routinely to the family physician before the child returned to his home after hospital or sanatorial care and after each clinic examination. The family physicians were informed that the children were being observed partly for research purposes, and the doctors were encouraged to seek consultation if the children should have symptoms or signs suggestive of a recurrence. The State University of Iowa ambulance service made it possible to transport the children back to the University Hospital for observation or treatment when indicated.

About two-thirds of the children lived in areas where local public health or school nursing service was available. An individual public health nursing report regarding the child was sent to the local public health nurse or school nurse before the child returned to his home after institutional care and after each clinic visit. The local nurse was advised to make home visits as often as she felt it was necessary, and to instruct the family to consult the family physician if any further difficulty should arise. The local nurses routinely sent reports to the clinic regarding the home care of the children.

PROCEDURE

In analyzing the recurrence rates of rheumatic fever for this randomized study group, we recognize that there are multiple factors on which the prevalence of rheumatic fever is dependent, and that these must be taken into consideration in evaluating the rates. Among those we have endeavored to control in our analyses or describe for the group are: the age of the subjects; the susceptibility of the group; the cyclic variation in the prevalence of the disease; and the severity of manifestations.

In analyzing statistically the data of recurrences with environmental factors for the association, chi-square is computed and the per cent of recurrence for different environmental factors is tabulated.

FINDINGS

Rate and Type of Recurrences.—The 266 patients were under observation a total of 893.5 person-years, between the ages of 4 to 21 years. For the age group 4 to 13 years, there were forty recurrences for 504.5 person-years of observation, or a rate* of 7.9 per cent; for the age period 14 to 16 years, there were twenty-four recurrences for 233.5 person-years of observation, or a rate

*The recurrence rate for a specified age period is the number of recurrences during the specified period divided by the number of person-years observed during the specific period. The quotient is multiplied by 100 to express in terms of per cent.

of 10.3; for the age period 17 to 21 years, there were seven recurrences for 155.5 person-years, or a rate of 4.5 per cent.

For the total group, seventy-one major and minor recurrences were experienced by fifty-one children. Table I shows the age-specific recurrence rates of rheumatic fever for children under our observation.

TABLE I. AGE SPECIFIC RECURRENCE RATES FOR 266 RHEUMATIC INDIVIDUALS COMPRISING 893.5 PERSON-YEARS OF OBSERVATION

AGE (YRS.)	PERSON-YEARS	RECURRENCE*	RECURRENCE WITH DEATH	RATE OF RECURRENCE (PER CENT)
4	6			0.0
5	16	1		6.2
6	30.5			0.0
7	44.5	1		2.2
8	56	5	1	10.7
9	61.5	2	1	4.9
10	64.5	5		7.8
11	73.5	10	1	15.0
12	75	8		10.7
13	77	5		6.5
4 to 13	504.5	37	3	7.9
14	82	5		6.1
15	80	9		11.2
16	71.5	10		14.0
14 to 16	233.5	24		10.3
4 to 16	738.0	61	3	8.7
17	60.5	4		6.6
18	48.5	1		2.1
19	32.5	2		6.1
20	12			0.0
21	2			0.0
17 to 21	155.5	7		4.5
4 to 21	893.5	68	3	7.9

*Major and minor episodes included; possible episodes not included.

The recurrence rate of Iowa-treated groups shows a significant deviation from the natural course of the disease. This difference is evidenced during childhood and is not present for the groups 14 years and older. Chart 1 compares the age specific recurrence rates of the Iowa study group of rheumatic subjects with rates derived by Wilson for a random sample of rheumatic subjects. There is a marked difference in the compared groups for the age period 4 to 13 years. From 14 to 21 years, the difference is not significant.

With few exceptions, the histories from the time of onset of rheumatic fever for each patient in the group are recorded. From the available histories, a study was made of the recurrence rate of two comparable groups, except for treatment, for the first year after onset. Both groups were from the same geographic area, belonged to the age group of 4 to 16 years, and had had a recent onset of the disease. In the group that received hospital treatment, there were 115 children under observation 108.5 person-years. In the group that was not treated by the hospital, there were 134 children with histories covering 128.5 person-years. The number of recrudescences (major, minor, and possible) for the groups, respectively, is 13 and 46, and the rate of recurrence for each group, respectively, is 12.0 and 35.8 per cent. For the hos-

pital-treated patients, chorea was the manifestation for six of the thirteen recurrences; for the patients receiving treatment elsewhere, chorea was the manifestation for fifteen of the forty-six recurrences. The difference in the recurrence rate for the treated and control groups of Iowa rheumatic patients is significant.

Table II compares specified recurrence rates of the study group with the rates as given by Wilson,[4] which reflect the expected rates of recurrence in a random sample of children with rheumatic fever:

TABLE II. RECURRENCE RATE OF RHEUMATIC FEVER OF SPECIFIED GROUPS

Within one year of previous attack	
4-16 years	
Iowa-control group, 134 patients	35.8 per cent
Wilson group	38.7 per cent
Iowa-treated group, 115 patients	12.0 per cent
Age specific	
4-13 years Iowa treated group	7.9 per cent
Wilson group	25.0 per cent
14-16 years Iowa-treated group	10.3 per cent
Wilson group	8.6 per cent
17-21 years Iowa-treated group	4.5 per cent
Wilson group	3.6 per cent

Of the ninety recurrences of the total group, forty-seven were major recurrences. This gives a rate for the major episodes for our group of patients observed between 4 to 21 years of 5.2 per cent.

Of the fifty-one children who experienced one or more recurrences under observation, three had carditis with no other manifestation, twelve had carditis in combination with other manifestations, two had polyarthritis and questionable carditis, seventeen had polyarthritis alone or in combination with some other manifestations but no carditis, five had chorea with some other manifestation but no carditis, and twelve had only chorea.

Of the fifteen children who had definite evidence of carditis, two were older children with pericardial effusion without evidence of myocardial or endocardial involvement. Of the remaining thirteen, eight had definite increase in heart involvement and increase in heart size (three of this group died), two had increase in heart involvement but no quantitative increase in heart size, one had an increase in heart size without progression of endocardial changes, one had endocardial changes but no residual increase in heart size, and one of the children has active rheumatic heart disease at the present time with increased involvement.

Of the three children who died, two had a severe recurrence within two months after leaving the sanatorium. One of these had marked cardiac damage from repeated attacks of the disease and died as a result of an acute infection with cardiac decompensation. No necropsy was made. The level of home care of this child was poor. The second of these three children was an 8-year-old girl who had developed severe myocarditis after measles (rubeola). She had no other manifestations of rheumatic fever and a diagnosis of toxic myocarditis had been made. Two months after leaving the sanatorium, the child became ill and was rehospitalized. She had definite evidence of myocarditis with decom-

pensation and died within a few days. A post-mortem examination revealed definite, active, rheumatic heart disease. The other child who died was under observation for over two years, and there was some difference of opinion as to whether the patient's disease was inactive. The child was less than 6 years of age when first seen at the clinic with his second attack of rheumatic fever. His disease remained active for about one year and at the end of this period of observation there were no signs of activity except the erythrocyte sedimentation rate readings had decreased only to within high normal range. On each subsequent out-patient examination, the erythrocyte sedimentation rate readings were slightly elevated but there were no other symptoms or signs of activity. The fatal recurrence occurred at home and no post-mortem examination was made.

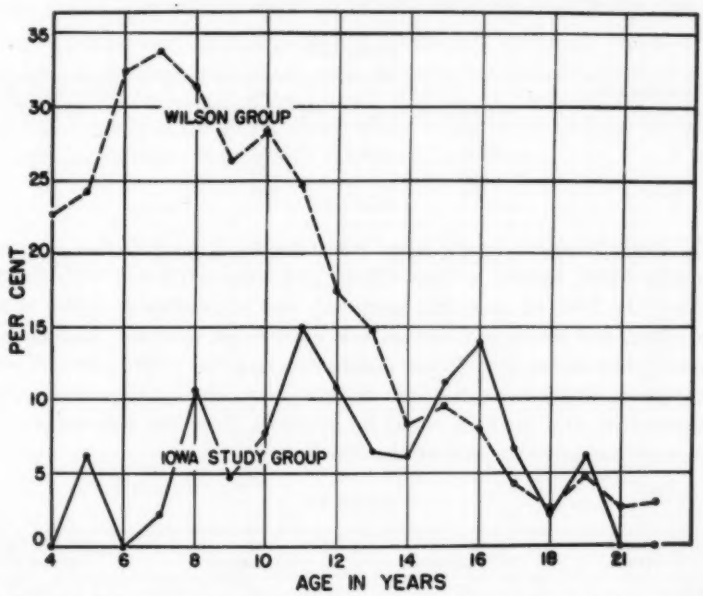


Chart 1.—Comparing the age specific recurrence rates of the Iowa study group of rheumatic subjects with the rates derived by Wilson for a random sample of rheumatic subjects. There is a marked difference in the compared groups for the age period 4 to 13 years. From 14 to 21 years, the difference is not significant.

Seventeen children experienced twenty-three recurrences in which chorea was the only manifestation. It was thought that a selective factor might very possibly bring an unusual number of choreic patients under our care and unduly weight our sample with this type of patient. A check of the number of patients having chorea at time of first observation showed that sixty-seven of 266 or 25.2 per cent had chorea at time of first visit. Jones and Bland[5] analyzed 1,000 consecutive cases of juvenile rheumatism at the House of the Good Samaritan in Boston and found that 28 per cent of all their cases had "pure chorea." It was concluded that this sample had a representative number of choreic patients.

AN EVALUATION OF THE RECURRENCES IN RELATION TO ENVIRONMENTAL FACTORS

The medical social worker appraised the economic and social situation of the home in which the patient lived after he came under care and supervision. The economic condition of the home was considered good when the income was sufficient to provide adequate diet, clothing, and shelter; fair when the income was marginal for diet, clothing, and shelter; poor when the income was not sufficient to provide adequate diet, clothing, and shelter. These ratings were available for 210 of the 266 patients.

Table III shows the number of children with recurrences and the number without recurrences for each of the three economic levels. Chi-square equal to .41 indicates no significant association between the distribution of the recurrences and the level of economic resources in the home.

TABLE III

HOME ECONOMIC SITUATION	RECURRENCE	NO RECURRENCE	TOTAL RHEUMATIC SUBJECTS
Good	9	37	46
Fair	19	65	84
Poor	21	59	80
Total	49	161	210

The social situation in the home was considered good if the parents were emotionally stable, sincere in their efforts, and cooperated well with the doctor; fair where the level of care was marginal, due to conditions which could not be controlled, and where cooperation was not always constant; and poor where the parents were either ignorant or indifferent, or both; where parental relationship was poor, where home life was disrupted, or where the parents could not help themselves, and no help could be obtained from the community. These ratings were available for 208 of the 266 homes.

TABLE IV

HOME SOCIAL SITUATION	RECURRENCE	NO RECURRENCE	TOTAL RHEUMATIC SUBJECTS
Good	3	27	30
Fair	18	65	83
Poor to fair	9	20	29
Poor	18	48	66
Total	48	160	208

Table IV shows the number of children with recurrences and the number without recurrences in the varying home social levels. Chi-square equal to 3.28 indicates an association between the distribution of the recurrences and the social situation, which is significant only at the 30 per cent level of confidence.

The third environmental factor rated for this rheumatic group is the dietary. The evaluation was made by one of the authors using the information obtained from histories taken at each clinic visit, from reports received from

the mothers, public health nurses, and social workers. The patients were classified into groups according to the way they followed the prescribed diet.

Good: Dietary advice adhered to at all times.

Fair: Dietary advice followed most of time; common errors were

(a) supplementary Vitamin D frequently omitted;
(b) child eating excessive amounts of unessential foods;
(c) limited selection of vegetables or fruits.

Fair to good: Fluctuations from fair to good.

Poor: Diet definitely low in one or more essential foods; the diets were most commonly low in protein, minerals, Vitamin D and the Vitamin B group.

Poor to fair: Fluctuating from poor to fair.

Very poor: Diet very inadequate; one or more essential foods absent.

These ratings were available for 251 of the 266 subjects. Table V shows the number of rheumatic children with recurrences and the number without recurrences in the various dietary levels. Chi-square equal to 18.45 indicates an association between the distribution of the recurrences and the dietary ratings which is significant with a high degree of confidence.

TABLE V

DIETARY	RECURRENCE	NO RECURRENCE	TOTAL RHEUMATIC SUBJECTS
Good	7	77	84
Fair to good	6	33	39
Fair	18	71	89
Poor to fair	10	11	21
Poor and very poor	7	11	18
	48	203	251

TABLE VI

ENVIRONMENTAL GROUP	RECURRENCES	
	NUMBER	PER CENT
Poor dietary	17 of 39	43.6
Poor home social	27 of 95	28.3
Poor home economic	21 of 80	26.2
Poor dietary and poor home social	14 of 29	48.2
Poor dietary and poor home economic	10 of 22	45.4
Poor home social and economic	18 of 69	26.1
Poor dietary, poor home social and economic	10 of 21	47.6
Fair dietary	18 of 89	20.2
Fair home social	18 of 83	21.7
Fair home economic	19 of 84	22.6
Fair dietary and fair home social	9 of 39	23.1
Fair dietary and fair home economic	8 of 34	23.5
Fair home social and economic	12 of 61	19.6
Fair dietary, fair home social and economic	8 of 32	25.0
Good dietary	13 of 123	10.5
Good home social	3 of 30	10.0
Good home economic	9 of 46	21.9
Good dietary and good home social	1 of 23	4.2
Good dietary and good home economic	5 of 31	16.1
Good home social and economic	3 of 28	10.9
Good dietary, good home social and economic	1 of 21	4.8

Table VI shows the presence of recurrences in different environmental groups.

The thirteen children who had recurrences with carditis comprise a group that suffered the serious effects of the disease. An analysis of their histories and environmental care shows that three of these children died within two months of their discharge from the sanatorium, and, in retrospect, there is doubt as to whether or not their disease was inactive. Their environmental care was fair or better, except for one boy who lived in a poor social situation. The ten children who survived with carditis, on the whole, lived in a poor home environment; all lived in poor social situations, seven in very limited economic circumstances, seven on a poor dietary, and three on a fair dietary.

Table VII shows the type of diet and level of home care received by the three children who died and by the ten children who had recurrences with carditis.

TABLE VII

LEVEL	HOME SITUATION		DIETARY
	ECONOMIC	SOCIAL	
	Three Children Who Died		
Good	1	0	2
Fair	2	2	1
Poor	0	1	0
	Ten Children With Carditis		
Good	1	0	0
Fair	2	0	3
Poor to Fair	0	3	3
Poor	7	7	4

DISCUSSION

An unexpectedly low recurrence rate is found for a highly susceptible group of young rheumatic children who have received special attention to improve their diets and level of home care. The management was more effective in lowering the recurrence rates in the younger children whose habits of living can be changed with less difficulty than the children approximately 14 years or more. The chances are greater also that younger children with the disease are living in a time in the family's existence when the burdens to be borne by the family are heaviest and consequently the needs of the child are met with greatest difficulty by many families.

Although the economic situation of the home for the study group showed no direct association with the distribution of the recurrences, our experience was that whenever poverty was present it was exceedingly difficult to provide the essentials of care, particularly an adequate diet. With outside help and supervision 33 per cent of the children in the poor economic group received a good diet and 36 per cent a fair diet.

Of the environmental factors rated, the most significant association is seen between the level of dietary care and the rheumatic recurrences. All ten of the children who had recurrences with carditis were receiving inadequate diets and living in poor social situations. It is known that the absence of good nutrition may induce a decreased resistance to bacterial infection. It seems a rea-

sonable hypothesis that improper nutrition may be one of the major factors which allows the host to respond abnormally to an infection. In our dietary data, the essentials most commonly deficient were protein, vitamin D, thiamine, and minerals. The dietary information was insufficient to allow quantitative computation, but the majority of the children were receiving inadequate diets at the time they developed their attack of rheumatic fever which brought them under our observation (Chart 2). The degree of deficiency of the diet appears to be related to the incidence and degree of heart damage.

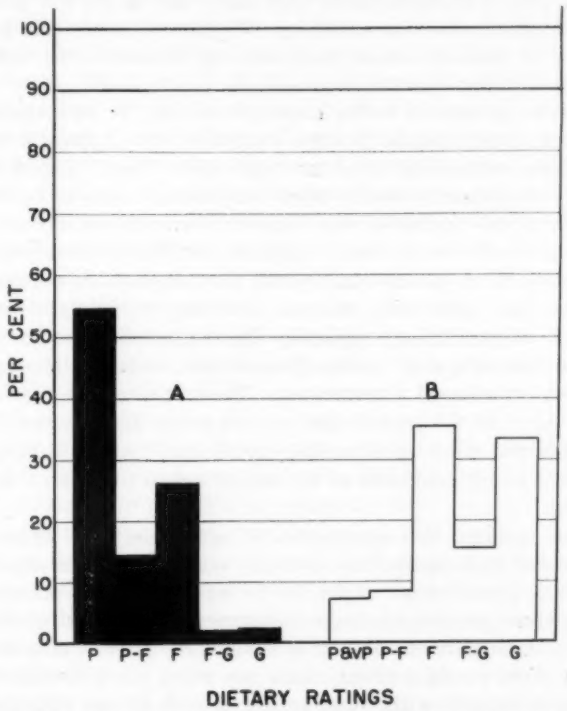


Chart 2.—The distribution of the dietary ratings of the rheumatic subjects (*A*) before observation and dietary instruction and (*B*) during observation and after dietary instruction. The area of each histogram to the left shows the proportion receiving the poorer dietary and to the right the better dietary.

It has been reported that the recurrence rate of rheumatic fever for a random sample is lower after puberty than before. The recurrence rate of our group after puberty was not significantly different from that reported for a random sample. The boys and girls who comprised the group (14 to 18 years) were those from whom little cooperation could be obtained because of the many instances of poor home social situations. The habits of living of these children were well established and they had the expected adolescent revolt against a supervised program. Our therapy probably was not given a chance to change the general situation or the course of the disease for many of the

group. The incidence of recurrences and of carditis for this group was as high as it was for any age period of our study group. All the adolescent children with carditis had poor diets and lived in poor home social conditions. For the 95.0 person-years observed from 18 to 21 years, there was no recurrence with carditis. The young adults with rheumatic fever in the armed services would fall into this older group. It is important to remember that carditis is more common during childhood and adolescence, when nutritional requirements are high. When the heights and weights of the rheumatic patients are plotted on growth charts, it has been noted that many fall in the out groups of body build, as undersized, obese, or tall-thin. We plan to study the growth charts further to see if these deviations have any significance in the light of the patients' dietary and history of disease.

The evidence presented in the literature is both for and against the existence of a definite correlation between nutrition and rheumatic susceptibility. The same is true concerning environmental care. Taran[6] found the incidence of recurrence of rheumatic fever after convalescent care to be four times as high in children who return to poor home environment as in those who return to good living conditions at home. Coburn and Moore[7] analyzed statistically data on the dietary of less susceptible and more susceptible rheumatic subjects. They found a close association between nutrition in childhood and rheumatic susceptibility. A preliminary report by the same authors on the results of reenforcing the diets of a small group of rheumatic children with eggs shows none of the subjects experienced a recurrence. These results were published pending further research. At the present time we are accumulating more detailed nutritional histories and biochemical studies on all new rheumatic subjects in order to correlate the nutritional state of the patients with the clinical manifestations of the disease.

We have classified the recurrences of our subjects as major, minor, and possible, in order to compare them with the reported rates in the literature. A more desirable classification might be to separate the recurrences into two groups; one, those patients having a recurrence with clinical evidence of carditis, and two, those patients having a recurrence without clinical evidence of carditis. In other words, segregate into one group the patients with proliferative signs as compared with those in the second group with only exudative manifestations.

The recurrence rate for major episodes for the accumulated reported groups of rheumatic patients who have received sulfonamide prophylaxis is 1.5 per cent. The recurrence rate for major episodes for our group of patients between 4 to 21 years is 5.2 per cent. However, these two groups of patients are not comparable, since the accumulated reported group of rheumatic patients who received sulfonamide prophylaxis included more patients of the older age group and chorea was excluded in some of the sulfonamide prophylactic groups. Chorea was a type of manifestation we found most difficult to prevent, and accounts for approximately one-sixth of the recurrences. The well-controlled groups reported by Kuttner,[8] however, are of children and the result of the treated as compared with the control group showed beyond doubt,

the prophylactic value of the drug. The rate is about one per cent for the sulfonamide prophylactic group. This author reports that the per cent of toxic reactions observed was fairly high, about 10 to 12 per cent. Stowell and Button[9] have reported the death of one child from agranulocytosis. Although toxic reactions from the use of small doses of sulfanilamide have been few and the reduction of rheumatic fever recurrences remarkable, nevertheless, sulfanilamide is by no means a harmless drug.

In addition to the toxic reactions from chemotherapeutic or antibiotic agents, there is also the danger that the host may lose his immunity to resist the organism and also the bacteria may become resistant to the drugs. Baldwin[10] has reported on the follow-up of a small group of children who had received chemoprophylaxis. She found no evidence of increased susceptibility to streptococcal infection and rheumatic activity at the time sulfanilamide was withdrawn. Epidemiology Units Numbers 22 and 89 of the Navy[11] and Damrosch[12] report the appearance of resistant strains of beta hemolytic streptococci after the use of sulfadiazine prophylaxis. Baldwin[13] also has reported that she did not observe the appearance of any sulfonamide resistant strains of streptococci in a group of rheumatic children treated prophylactically with sulfadiazine.

It is feared, since sulfonamide drugs have been found to offer a simple means of preventing recurrences of rheumatic fever, that more indifference to the problems of environmental care will follow. This study indicates that every effort should be made to tackle the problem of improving the general living conditions of these children. It requires much more time, knowledge, and patience to instruct the mother how to care for and feed her child than to instruct her how to give a few pills each day. It is usually easier for the social worker to obtain medication for an indigent child than to arrange for a satisfactory level of home care including an adequate diet.

Families who have been helped to provide a high level of environmental care for their children should have fewer siblings develop the disease. The next generation of children also should have a lower incidence of rheumatic fever. Studies of groups of rheumatic patients should evaluate not only the recurrence rate of the group but also the social adjustment of the children. Children given opportunity for more wholesome relationships, better diet, and outside attention make remarkable physical, emotional, and intellectual growth.

Some rheumatic children will come under observation who are forced to live in unfavorable environments, and these children should definitely be given the benefit of sulfonamide prophylaxis, particularly those of this group with definite valvular heart disease and cardiac enlargement should be given this added protection.

SUMMARY AND CONCLUSION

The recurrence rate of rheumatic fever in this study group of rheumatic subjects who received special attention to improve their diets and level of environmental care is significantly different from that reported by Wilson for a random sample and from a comparable Iowa group that did not receive improved environmental care the first year after onset. The recurrence rate for

the study group was lower for the age group 4 to 13 years and slightly higher or the same for the older age groups. It is noteworthy that the age from 4 to 13 years is a period in which nutritional requirements of the child are high and a time in the child's life when his habits of living can be controlled with less difficulty than from approximately age 14 years and older. The most significant association between the environmental factors and the distribution of the recurrences was found for the dietary factor. These data do not indicate with a high degree of confidence that there is an association between the distribution of the recurrences and the home social situation. However, the extreme social situation groups show significant differences in the per cent of recurrences favoring better social environment, and all children who had recurrences with carditis lived in poor social situations. The distribution of the recurrences did not show any association with the family's economic level. The dietary ratings of the group are related to the economic levels, but even in the poor economic level, more received good or fair diets (33 per cent and 26 per cent) than would have been expected without outside supervision and help.

Every precaution must be taken to be certain the disease is inactive before liberating the child and depending on a high level of environmental care to protect the child from further attacks. The major recurrence rate, although low, was higher than the rate for patients treated with sulfonamide prophylaxis. It was concluded that if the disease is definitely inactive, an excellent diet and wholesome living conditions will practically eliminate the chances of a recurrence with carditis; and that sulfonamide prophylaxis is indicated for children recovered from rheumatic fever who have had definite carditis and are forced to live in an environment which does not provide a good diet and at least a fair level of general care.

REFERENCES

1. Jones, T. D.: J. A. M. A. **126**: 481, 1944.
2. Taran, L. M.: J. PEDIAT. **29**: 77, 1946.
3. Hansen, A. E.: J. PEDIAT. **28**: 296, 1946.
4. Wilson, M. G., and Lubschez, R.: J. A. M. A. **126**: 477, 1944.
5. Jones, T. D., and Bland, E. F.: J. A. M. A. **105**: 571, 1935.
6. Taran, L. M.: J. PEDIAT. **18**: 737, 1941.
7. Coburn, A. F., and Moore, L. V.: Am. J. Dis. Child. **65**: 744, 1943.
8. Kuttner, A. G., and Reversbach, G.: J. Clin. Investigation **22**: 77, 1943.
9. Stowell, D. D., and Button, W. H.: J. A. M. A. **117**: 2164, 1941.
10. Baldwin, J. S.: J. PEDIAT. **30**: 67, 1947.
11. Epidemiology Unit No. 22: J. A. M. A. **129**: 921, 1945.
12. Damrosch, D. S.: J. A. M. A. **130**: 124, 1946.
13. Baldwin, J. S.: J. PEDIAT. **30**: 288, 1947.

A REVIEW OF THE SUBJECT OF CONGENITAL HEMIHYPERTROPHY AND A COMPLETE CASE REPORT

JOHN WARD, M.D. AND HENRY H. LERNER, M.D.
SALT LAKE CITY, UTAH

HEMIHYPERTROPHY is defined as hypertrophy or overgrowth of one-half or one side of the body.[1] Total hemihypertrophy specifically indicates that the overgrowth includes all of the systems: muscular, vascular, neurologic and skeletal. This entity should be differentiated from hemiatrophy, wherein there is comparative smallness of one half of the body due to a lesion of the post-central gyrus.[2]

Anatomic observations in both the living and the cadaver have established the fact that symmetry of the two halves of the body does not exist (Halperin, quoting Meckel).[3] This was recognized by the sculptors of Greece and Rome, whose statues, being modeled after living subjects, showed such awareness long prior to the descriptions of anatomists. Moderate asymmetry is so common that it is not considered significant. The only reports to reach the literature are those in which this finding is unusually prominent.

LITERATURE

Interest in hemihypertrophy was first stimulated in 1822 by the anatomic studies of Meckel pointing out the variations in size and shape of the right and left halves of the body.[3] In 1839 the first clinical study of a patient with hemihypertrophy was reported by Wagner[9] and was soon followed by the reports of Desvouges and associates.[7] Liebriech,[3] in 1908, pointed out that asymmetry of the face and skull is the characteristic finding in the human species. In 1921 and 1927 Gesell[4, 5] reviewed the literature and discussed fully the current theories as to the etiology of hemihypertrophy. Lenstrup,[6] in 1926, and Wakefield and Hines,[7] in 1933, re-evaluated all of the reported cases. By 1939, Petre[8] noted that there were 103 cases in the world literature. In 1942, Schwartzman and Grossman,[9] after critically analyzing Petre's paper, stated that only 101 of these cases fitted the true total hemihypertrophy category. They added one case of their own. Since then, additional cases have been reported by E. Toussaint Aragon,[10] Sayer and Fatherree,[14] and Rugel[11] bringing the total to 105. We are reporting the one hundred and sixth case. In the literature there are only seven cases mentioned as including a complete necropsy protocol.[11, 18, 21, 27, 31-33] This will make the eighth.

INCIDENCE

Actual statistics as to the incidence of mild forms of asymmetry have not been given much prominence, in view of the fact that it is evident to some degree in all individuals. Marked asymmetry is probably much more common than a review of the literature would indicate.

From the Department of Radiology, University of Utah School of Medicine.

Hemihypertrophy has been described as early as a ten mm. embryo and has been demonstrated quite frequently at birth.[7] Detection in infancy depends on the sensitization of the observer to the existence of such an entity. In many of the cases both halves of the body grow paripassu until puberty, at which time the malformation may become accentuated.[9] Males are more commonly affected than females.[5, 7, 13] Its apparent rarity in the Negro is probably weighted by the fact that most of the reports come from institutions with a low Negro population. On the other hand, Halperin[3] states that anatomic studies reveal the incidence of asymmetry to be lower in the Negro than the white race.

CLASSIFICATION

The literature is confusing in its designations and definitions when referring to the subject of total hemihypertrophy. The entity has been designated by various authors under the following names: "true total hemihypertrophy,"[19] "unilateral hypertrophy,"[13] "congenital hypertrophy,"[14] "hemigigantism,"[15] "hemihypertrophy totalis,"[16] "hemimacrosomia,"[20] and "partial gigantism."[19] Statistical evaluation of the cases reported is almost impossible because of the incompleteness of protocols and the lack of a uniform descriptive terminology.

Stoesser[20] first attempted to clarify the situation by proposing the following classification:

I. True hypertrophy
  A. Congenital hypertrophy
    1. Partial hypertrophy
      (a) Hemihypertrophy
      (b) Crossed type of hypertrophy
    2. Total hemihypertrophy
  B. Acquired hypertrophy

II. False hypertrophy
  A. Congenital hypertrophy
    1. Milroy's disease
    2. Elephantiasis
    3. Hemihypertrophy
  B. Acquired (elephantiasis)

This classification would be acceptable, except that it does not provide for inclusion of those cases in which the hypertrophy is not total but is limited to one or several systems. We should like to suggest a more complete classification.

HYPERTROPHY

Congenital

I. Total hypertrophy (involving all systems)
  A. Segmental
  B. Crossed
  C. Hemihypertrophy

II. Limited Hypertrophy (in which one or more but not all systems are involved.)
- A. Muscular
- B. Vascular
- C. Skeletal
- D. Neurologic

Acquired

I. Total Hypertrophy
- A. Gigantism—hyperpituitarism
- B. Neurofibromatosis

II. Limited Hypertrophy
- A. Milroy's disease
- B. Elephantiasis
- C. Lipomatosis
- D. Neurofibromatosis
- E. Vascular anomalies
- F. Multiple A-V aneurysms

Congenital hypertrophy is differentiated from the acquired type in that the overgrowth is detectable at birth and originates in some developmental abnormality early in the growth of the ovum. To be classified as total hypertrophy all of the systems (neurologic, muscular, skeletal, and vascular) must be shown to be involved. Segmental hypertrophy refers to those cases wherein the involvement is limited to a digit, an extremity, one-half of the skull, or a portion of the trunk. Overgrowth of one half of the body and one or more segments of the other half is designated as crossed hypertrophy. Hemihypertrophy designates involvement of one entire half of the body in the overgrowth process. Limited hypertrophy represents a systemic delimitation of the process.

The acquired hypertrophies are obvious and need no explanation.

The particular entity which we are reporting is designated according to our classification as congenital total hemihypertrophy.

ETIOLOGY

A multitude of etiologies have been suggested in the literature in an attempt to explain the origin of congenital total hemihypertrophy. Endocrine factors,[9, 21] congenital syphilis,[9] vascular lesions,[9] abnormalities of the lymphatic system,[9, 23] lesions of the brain,[9] embryonic defects of the vegetative nervous system,[9] mechanical influences,[9] heredity, and embryogenic variants have all been incriminated. Abnormal function of the pituitary and adrenal glands[21] have been ascribed as a cause. Roentgenograms of the skulls of these patients have failed to demonstrate any abnormality of the pituitary fossa.[3, 7, 19, 22] Postmortem examination of the pituitary gland[11, 13] has been unproductive. Although enlarged adrenals have been observed on the involved side at autopsy,[21] no clinical evidence of dysfunction of this gland has been recorded. Because of their frequent association with this entity, vascular lesions have been suggested

as the cause of hemihypertrophy.[4, 9, 22] It is known that arteriovenous aneurysms can cause true hypertrophy. In cases of congenital total hemihypertrophy, vascular lesions such as nevi and telangiectasis often occur on the contralateral side.[4, 9] Disturbance of the lymphatic system[4, 9, 23] have been suggested as the cause of this hypertrophy because of its superficial resemblance to elephantiasis and idiopathic lymphedema (Milroy's disease).

Lesions of the central nervous system are known to cause hemiatrophy, which is often confused with hemihypertrophy.[2] Cases of total hemihypertrophy which have come to autopsy failed to reveal any central nervous system involvement.[3] Mechanical influences (such as pressure on the developing ovum or fetus) have been shown experimentally to influence growth. In these instances hemiatrophy is expected rather than hypertrophy.

The relationship of skeletal overgrowth in association with neurofibromatosis has been reported.[12, 17] A definite segmental overgrowth in relation to the affected nerve was pointed out, suggesting that the presence of the abnormal nerve structure resulted in overstimulation and consequent overgrowth of the extremity. The overgrowth was mixed (over- and underdevelopment), representing lack of control rather than stimulation of growth. Although this theory is fascinating, none of the autopsied cases in the literature of congenital total hemihypertrophy have revealed evidence of neurofibromatosis.[3] Schwartzman and Grossman[9] by the use of atropine, adrenalin, and pilocarpine, were unable to detect any changes in the vegetative nervous system of the hypertrophied side as compared to the normal.

Gesell[4, 5] feels that an imbalance of the normal process of twinning is involved in hemihypertrophy. The idea is advanced that it represents a physiologic isolation of equivalent parts of the blastoderm. One side of the two bilateral primordia is thought to be subjected to an inequality so that at first physiologic independence and later actual physical change is manifested.

Heredity has received little note as an etiologic factor. Scott[13] reports the occurrence of hemihypertrophy in a mother and daughter, and Reed[28] reported its appearance in a brother and sister.

The whole gamut of abnormalities is obviously possible. The numerous developmental anomalies which are often seen in association with hemihypertrophy probably represent related facets of this entity.

FINDINGS

Mental deficiency is often the presenting complaint. This is said to occur in from 15 to 20 per cent of cases.[7, 9] Physical and mental measurements usually show that the condition once developed remains relatively constant. The gross asymmetry is usually obvious. The hypertrophied parts appear to be edematous although the skin may feel normal in texture. In some instances it has been described as being thickened. The range of hypertrophy may vary from the simple overgrowth of a digit to complete hypertrophy of one-half or more of the body.[5] It may involve an extremity, half of the skull, or half of the thorax. The asymmetry of the skull resembles that seen in hydrocephalus. The hair on the enlarged side is thickened. The pupil on the involved side is frequently

larger than the opposite one. The vessels of the involved side may be unduly prominent. Nevi and telangiectasia are often seen. The right side is more frequently involved than the left.[5, 7, 9] Unilateral enlargement of a part or parts is usually overlooked until some difficulty is met in obtaining shoes or gloves that fit both extremities equally well. If the overgrowth is markedly prominent, the individual's appearance may become grotesque. Deformities of the feet (macrodactyly or polydactyly), scoliosis, tilting of the pelvis with associated limping, and sciatica have been noted.[7, 14, 26]

In 50 per cent of the cases there are associated abnormalities.[5, 9] Many of these are cosmetic defects which bring the patient to the physician. These deformities include abnormal nail growth,[13] premature eruption of teeth,[13] excessive secretion of sebaceous and sweat glands,[13, 29] thickening of hair on the involved side,[4, 11, 29, 30] telangiectasia,[3] early appearance of varicose veins,[3] clubbed feet,[13] hypospadius,[7] cryptorchidism,[7] congenital heart disease,[7] polydactylism,[7] nevi,[5, 7, 13, 24] supernumerary nipples,[15, 25] syndactylism,[4] pigmentation of skin,[14] enlargement of the tonsil,[3] and hypertrophy of one of the paired organs on the involved side.[7] On opening the body, enlargement may be found on the hypertrophied side.[18, 31-33] This usually involves the kidney and adrenal gland. No involvement of the central nervous system or pituitary gland has been recorded.[3, 31]

The microscopic picture reveals true hypertrophy in all the systems. There is an overgrowth of the media and intima of the blood vessels,[13, 31] and the muscle bundles are larger than normal.[26] The bones also show overgrowth.[18, 31-33] Hypertrophy of the interstitial connective tissue of the peripheral nerves is likewise described.[13]

CASE REPORT

B. O., an 8-month-old, white, male infant was referred to the Salt Lake General Hospital, Pediatric Division, for therapy of meningitis.

The child was born spontaneously after a normal labor of seven hours; breathing immediately following delivery. Shortly after birth, it was observed that the right side of the infant's body was noticeably larger than the left. It was also noted that the infant had six toes on the right foot. The supernumerary digit was removed and was remarked to be highly vascular. The superficial blood vessels of the skin appeared more prominent on the right than on the left. On occasions the right side of the body would become "purple," while the left half would remain relatively normal in color. The mother stated that at 8 months the child had never sat up or crawled. The patient had been perfectly well until the onset of meningitic symptoms one week before entry into the hospital. The family history was negative for any congenital anomalies or twins.

Physical Examination.—The child was found to be acutely ill and comatose. Temperature was 101° F., pulse 140, respirations irregular. The neck was stiff and the head was kept turned to the right. The right side of the body, including the skull and extremities, was enlarged as compared to the left. Prominent veins were observed on both sides of the scalp (more marked on the left). The remainder of the examination was normal.

Laboratory Data.—Lumbar puncture revealed a cell count of 102 cells per cubic millimeter with 78 per cent polymorphonuclears and 22 per cent lymphocytes. The protein was 114 mg. per cent and quantitative sugar less than 20 mg. per cent. Blood and spinal fluid cultures were negative.

In spite of intensive fluid and chemotherapy, the patient expired the day following admission before further clinical studies could be completed.

Measurements during life:

Height	68 cm.
Circumference of the head	47 cm.

	Right (cm.)	Left (c.m.)
Length of arm	17.0	16.0
Length of forearm	8.5	8.5
Length of leg (knee to ankle)	12.5	12.0
Circumference of forearm	14.5	12.75
Circumference of thigh	20.0	18.0
Circumference of calf	17.0	15.5

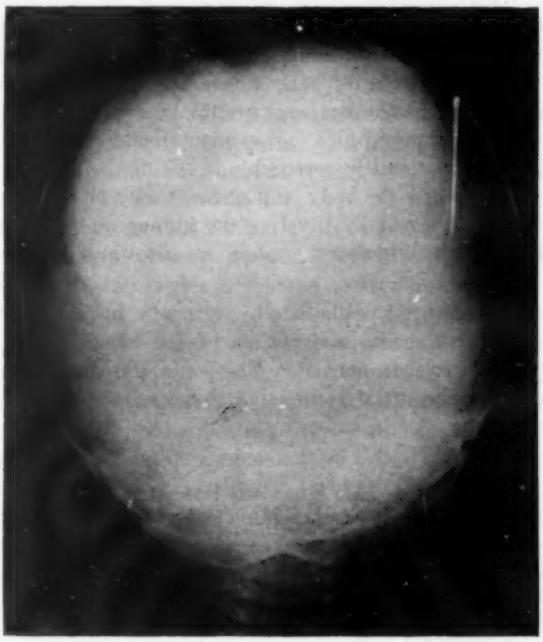


Fig. 1.—The right half of the skull is larger than the left.

Roentgenograms.—(Immediately after expiration.) There was moderate enlargement of the right half of the skull. The suture lines were normal and there was no evidence of increased intracranial pressure (Fig. 1). The chest (Fig. 2) showed nothing unusual except that the layers of the soft-tissue shadows on the right side of the body appeared to be wider than those on the left. This was also evident in the abdomen (Fig. 2). The upper (Fig. 3) and lower extremities (Fig. 4) demonstrated the marked increase in the size of the soft-tissue shadows on the right.

Measurements: (length)	*Right* (cm.)	*Left* (cm.)
Humerus	8.0	7.3
Ulna	7.2	7.1
Radius	6.7	6.3
Femur	11.3	11.1
Tibia	8.6	8.5

NECROPSY REPORT*

External Appearance.—The body was that of a well-nourished male infant, measuring 68 cm. in length. There was striking asymmetry of the body, including head, trunk and extremities. The entire right side of the head was larger than the left side. The frontal boss of the right side was particularly prominent and the right side of the face appeared to droop below the level of the left side. The anterior fontanel measured 5 cm. in its greatest diameter and the posterior fontanel was nearly closed. The hair had been shaved from the left half of the scalp and numerous small linear hemorrhages were visible through the epidermis of the shaved area. The circumference of the head over the frontal bosses and occiput was 64.7 cm. The irises were dark blue, the pupils round and equal in size, and the conjunctiva were pale. The lower jaw was rigid and a small quantity of frothy fluid exuded from the mouth. The visible portions of the buccal mucosa were pale.

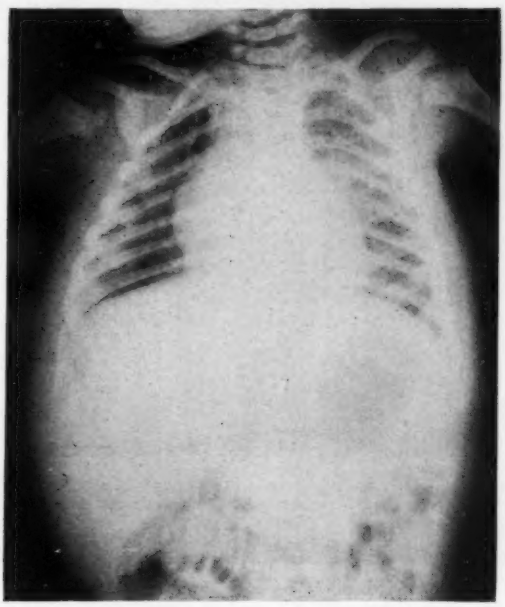


Fig. 2.—There is an increase in the thickness of the soft-tissue shadows of the right half of the thorax and abdomen as compared to the left.

The cervical lymph nodes were not palpable. There was slight greenish-gray discoloration of the skin of the trunk and punctate hemorrhages, surrounding needle puncture holes, were present on both sides in the upper anterior part of the thorax. The penis showed orange-red discoloration and appeared to be superficially excoriated.

The right upper extremity was longer and had a greater diameter than the left. The over-all length of the right was 22 cm. and of the left, 20 cm. The right lower extremity measured 23 cm. in length and the left measured 21 cm. In an incision through the skin and subcutaneous tissue of the anterior surface of each thigh, the fat measured 0.8 cm. in thickness on the right side and 0.5 cm. on the left.

Primary Incision.—The subcutaneous fat in the midline measured up to 0.5 cm. in thickness. Upon palpation, the abdominal wall was found to be slightly thicker on the right side than on the left. No abnormalities of the muscles were noted.

*Dr. Crichton McNeil, University of Utah School of Medicine.

Body Cavities.—The peritoneal cavity contained no free fluid and the viscera were in normal position. Approximately 50 c.c. of clear fluid were found in the left pleural cavity, but no excess of fluid was present on the right side. The pericardial sac contained an estimated five c.c. of clear fluid.

The ribs appeared to be normal. There was slight anterior bowing of the thoracic spine between the levels of the fifth and twelfth vertebral bodies. The lumbar vertebrae showed no abnormality.

Fig. 3.—Roentgenograms showing a marked increase in the soft-tissue shadows of the right upper extremity as compared to the left. This is most marked in the region of the subcutaneous fat.

Thymus.—The position was normal, and the thymic tissue was estimated to weigh about 5. gm.

Thyroid Gland.—Apparently normal.

Heart.—The position and shape were normal. Weight was not recorded. The circumferences of the valves were: pulmonary, 2.5 cm.; tricuspid, 3.5 cm.; aortic, 2.0 cm.; and mitral, 3.0 cm. The right ventricular wall measured .02 cm. and the left ventricular wall 0.8 cm. in maximal thickness. The endocardial surfaces and the valves appeared normal. The myocardium was pale but not otherwise remarkable.

Lungs.—The right lung weighed 65 Gm. and appeared to be entirely normal. The interlobar fissures were well formed. The left lung weighed fifty Gm. and appeared to be normal, with the exception of a few small hemorrhages on the pleural surface.

Spleen.—The capsular surface was smooth and dark purple-red. The weight was 25 Gm. On sectional surfaces the pulp was dark raspberry-red.

Pancreas.—The over-all length was 8 cm. and the greatest diameter was about 1 cm. On section, the lobular structure appeared to be entirely normal.

Liver and Gall Bladder.—Total weight was 275 Gm. The capsular surface was dull and the parenchyma tended to bulge slightly at the margins of the incised capsule. Sec-

tional surfaces were dull; pale tan and lobular markings were indistinct. The lumen of the gall bladder contained about 5 c.c. of clear, pale-yellow bile.

Stomach and Intestine.—The stomach was approximately normal in size and shape. The mucosal rugae were flattened out. The duodenal mucosa was stained yellowish, and the lumen of the entire small intestine contained yellow chyme. The appendix appeared normal upon gross inspection. The lumen of the colon contained only a small quantity of yellowish-brown formed feces. The mucosa was normal in appearance throughout.

Fig. 4.—There is a marked increase in the size of the soft-tissue shadows of the right lower extremity as compared to the left.

Genitourinary Tract.—The kidneys were about equal in size and weighed about 50 Gm. each. The cortical surfaces were smooth and showed persistent fetal lobation. The cortex measured about ½ cm. in thickness and bulged slightly at the margins of the incised capsules. The lining of pelves and calyces appeared to be normal, the ureters were patent and of normal diameter. The urinary bladder measured about 3 cm. in diameter, and its lining was not remarkable.

Head.—The asymmetry of the skull included the base as well as the calvarium; the base also was appreciably larger on the right side.

When the dura mater was removed, there was an escape of cloudy cerebrospinal fluid. There was abnormal opacity of the leptomeninges of the entire convexity, especially along the courses of the blood vessels in the sulci, apparently due to infiltration by purulent exudate. The infiltration also involved the base of the brain and was particularly dense in the region of the larger vessels.

After fixation, the brain weighed 1,375 Gm. Clotted blood filled the lumens of both posterior cerebral arteries. In multiple frontal sections the brain substance appeared to be edematous and was softer than normal. The lateral ventricles were moderately dilated. Numerous red points resembling perivascular hemorrhages were found in the region of the basal ganglia on both sides and in the brain stem at the level of the superior colliculi. One small focus of discoloration in the left occipital lobe resembled an abscess.

MICROSCOPIC FINDINGS

Brain.—(Including cerebral cortex, midbrain, pons, and medulla.) The principal pathologic alteration consisted of diffuse proliferation of the reticulum cells of the arachnoid. There was also infiltration of its interstices with large mononuclear cells (many of a macrophagic type), small mononuclear cells including lymphocytes and plasma cells, and a relatively large number of polymorphonuclear neutrophiles. In a few places there was evidence of beginning organization of the exudate in the form of dense masses of fibroblast-like cells. In the region of the basilar artery, dense zones of small lymphocytes partly surrounded the vascular spaces. The only alteration of the brain substances was slight perivascular edema which was most pronounced in the cortical gray substance. No abscess formation was found in the sections examined.

Heart.—The myocardium showed no significant alterations. The endocardium and pericardium were thin and smooth.

Lungs.—Slight intralveolar edema.

Thymus.—Differentiation between cortex and medulla was lacking. Lymphoid cells were relatively scanty and were diffusely but irregularly scattered throughout the glandular substance. Hassell's corpuscles were apparently normal. The capsule and trabeculae appeared edematous.

Thyroid.—Not remarkable.

Spleen.—Essentially normal.

Pancreas.—Apparently normal.

Liver.—Advanced parenchymatous degeneration and necrobiosis of the parenchyma in the central zones with slight leucocytic infiltration.

Adrenals.—The cortical zones were well demarcated. The cortex appeared thinner than normal (averaging approximately ½ mm.) but was otherwise not remarkable.

Kidneys.—Mild diffuse parenchymatous degeneration and focal advanced degeneration of a few tubules apparently of the distal convoluted portion. Occasionally a small focus of fibrinoid degeneration of the glomerular tufts was seen.

Skin.—The vessels were more prominent in the subcutaneous tissue on the right. The prominence was due to medial hyperplasia of all the vessels, especially of the arterioles.

PATHOLOGIC DIAGNOSIS AND SUMMARY

1. Unilateral hypertrophy of the somatic tissues of the body, including the right side of the skull, right cerebral hemisphere, right side of the body wall, and right upper and lower extremities.
2. Diffuse purulent leptomeningitis (nonhemolytic streptococci).
3. Acute parenchymatous degeneration of the liver and kidneys.
4. Thrombosis of both posterior cerebral arteries.

The *chief diagnosis* was acute purulent leptomeningitis.

DISCUSSION

The only condition which might be mistaken for hemihypertrophy is the one of hemiatrophy due to brain injury. In the latter, neurologic disturbances due to degenerative changes are demonstrable, whereas the former is associated with developmental anomalies.

The presence of a supernumerary toe and the abnormal vascularity facilitated the early detection of the hemihypertrophy at birth. The diagnosis depends on the sensitization of the examiner to the entity. Often, it escapes recognition until marked physical or mental abnormalities are produced.

The "purplish" discoloration on one side of this child's body worried the mother. The possibility of subnormal mental development, suggested by the fact that the baby never cried, crawled, or sat up, caused no concern. It was used to label the child an "exceptionally good baby."

If the hemihypertrophy and supernumerary toe had not been noted at birth, the question of wthe meningitis contribution to the development disturbance might be raised. However, this is obviously not to be considered in this case.

There is no suggested etiologic factor which satisfactorily explains all the variations seen with hemihypertrophy. The theory of an imbalance of normal twinning is the most accepted explanation to date.

SUMMARY

1. The literature pertaining to hemihypertrophy is reviewed.
2. A more applicable classification is suggested.
3. The etiologic, clinical, and pathologic findings are discussed.
4. A case of congenital total hemihypertrophy with necropsy findings is reported.

REFERENCES

1. Dorland, W. A. N.: American Illustrated Medical Dictionary. W. B. Saunders Co., 1944, Philadelphia.
2. Penfield, W., and Robertson, J. S. M.: Growth Asymmetry Due to Lesions of Postcentral Cerebral Cortex, Arch. Neurol. and Psychiat. **50**: 405, 1943.
3. Halperin, G.: Normal Asymmetry and Unilateral Hypertrophy, Arch. Int. Med. **48**: 676, 1931.
4. Gesell, A.: Hemihypertrophy and Mental Defect, Arch. Neurol. and Psychiat. **6**: 400, 1921.
5. Gesell, A.: Hemihypertrophy and Twinning; Further Study of Nature of Hemihypertrophy with Report of New Case, Am. J. M. Sc. **173**: 542, 1927.
6. Lenstrup, E.: Eight Cases of Hemihypertrophy, Acta. Pediat. **6**: 205, 1926.
7. Wakefield, E. G., and Hines, E. A., Jr.: Congenital Hemihypertrophy; Report of Eight Cases, Am. J. M. Sc. **185**: 493, 1933.
8. Petre, A., Schere, S., and Pellerano, J. C.: Congenital Hemicorporal Dysharmonies, Arch. argent. de pediat. **10**: 294, 1939.
9. Schwartzman, J., Grossman, L., Dragutsky, D.: True Total Hemihypertrophy, Arch. Pediat. **59**: 637, 1942.
10. Aragon, E. Toussaint: Left Total Congenital Hemihypertrophy; Case, Rev. mex. de pediat. **12**: 343, 1942.
11. Rugel, S. J.: Congenital Hemihypertrophy, Am. J. Dis. Child. **71**: 530, 1946.
12. Lehman, E. P.: Recklinghausen's Neurofibromatosis and Skeleton, Arch. Dermat. and Syph. **14**: 178, 1926.
13. Scott, A. J.: Hemihypertrophy; Report of Four Cases, J. PEDIAT. **6**: 650, 1935.
14. Sayer, A., and Fatherree, T. J.: Congenital Hemihypertrophy; Report of a Case, U. S. Nav. M. Bull. **44**: 142, 1945.
15. Wiseberg, M.: Unusual Case of Hemigigantism, Canad. M. A. J. **25**: 591, 1931.
16. Crosby, E. H.: Hemihypertrophy Totalis; Case Report, J. Bone and Joint Surg. **17**: 1025, 1935.
17. Moore, B. H.: Some Orthopedic Relationships of Neurofibromatosis. J. Bone and Joint Surg. **23**: 109, 1941.
18. Hofmann, Max: zur Pathologie des Angeborenen Partiellen Riesenwucheses Bietr. Z. klin Chir **48**: 391, 1906.
19. Barr, D. P.: Congenital Hemihypertrophy and Partial Gigantism, J. Missouir M. A. **26**: 298, 1929.

20. Stoesser, A. V.: Hypertrophies of Infancy and Childhood, Am. J. Dis. Child. 35: 885, 1928.
21. Hutchison, R.: Hemihypertrophy, Proc. Roy. Soc. Med., Lond., 9: Sect. Stud. Dis. Child, 1915-16.
22. Harwood, J., and O'Flynn, E.: Right Sided Hemihypertrophy Associated with Pubertas Praecox, Proc. Roy. Soc. Med. 28: 857, 1935.
23. McFarland, B. L.: Hemihypertrophy, Brit. M. J. 1: 345, 1928.
24. Glanzer, J.: Total Unilateral Hypertrophy, Am. J. Dis. Child. 45: 1056, 1933.
25. Landauer, W.: Supernumerary Nipples, Cong. Hemihypertrophy, and Cong. Hemiatrophy, Human. Biol. 11: 447, 1939.
26. Hench, P. S., Wakefield, E. G., and Camp, J. D.: Postural Sciatica in Association with Congenital Hemihypertrophy, M. Clin. North America 15: 1497, 1932.
27. Gordinier, H. C.: Case of Unilateral Hypertrophy of the Whole Left Side with Autopsy, Albany M. Ann. 39: 47, 1918.
28. Reed, E. A.: Congenital Total Hemihypertrophy, Arch. Neurol. and Psychiat. 14: 824, 1925.
29. Mayers, L. H.: Hemihypertrophy, Surg. Gynec. & Obst. 43: 746, 1926.
30. Lisser, H.: Congenital Total Hemihypertrophy, J. A. M. A. 82: 1046, 1924.
31. Cagiati, Luigi: Klinischer und pathologischer Bietrag zum Studium der halbseitigen Hypertrophie, Deutsche Ztschr. f. Nervenh. 32: 282, 1907.
32. Arnheim, G.: Ueber einen Fall von congenitalen halbseitiger Hypertrophie mit angeborenen bronchiectasien, Virchows Arch. f. path. Anat. 154: 300, 1898.
33. Hornstein, S.: Ein Fall von halbseitigem Riesenwuchses. Virchows Arch. f. path. Anat. 133: 440, 1893.

SOME FACTORS WHICH INFLUENCE THE DURATION OF BREAST FEEDING

MILDRED A. NORVAL, M.D.*
ROCHESTER, MINN.

THIS report is concerned with the relationship of certain maternal and infant factors to the duration of breast feeding. The maternal considerations were age, number of living children, the amount and duration of breast engorgement, and the urban or rural dwelling place of the mother. The only factor considered in the baby was the weight at birth. None of these factors can be considered as entirely independent of the psychologic attitude of the mother toward breast feeding. However, in this particular group of mothers, all expressed the desire to breast feed their infants, so that this attitude probably is of less importance here than in the usual cross-section of mothers.

It has been stated[1-4] that defective lactation occurs most often in primiparas more than 30 years old and in those who are very young. Hamill quoted van Swieten[5], who said that the optimal age for wet nurses was between 25 and 30 years. Stewart and Pratt[4] found that the incidence of complete breast feeding decreased as the age of the mothers increased. Others[6,7] have found that the age of the mother made no difference in her ability to nurse an infant.

Multiparous women are believed by some[5,8] to have more milk than primiparous women. Martin[9] found, among 10,178 mothers who nursed their infants, that 40 per cent were primiparas and 52 per cent were multiparas. Others[4,10] believe that parity does not influence lactation.

Almost nothing is found in the literature concerning the onset or amount of engorgement and its relationship to lactation. Hamilton[11] said that delay in the appearance of engorgement is no indication that breast feeding will be unsuccessful. McNeil[12] found that difficulties in lactation arose when massive, early engorgement occurred.

Many have written about the effect of emotional states[1, 3, 4, 13, 14] and fatigue[15] on the secretion of breast milk. Darner and Hunter[16] found that 18 per cent more mothers were able to supply breast milk for their babies if no visitors were allowed during the hospital stay. Worcester[14] said that the social demands on modern mothers conflict with the babies' right to suckle. He felt that too many mothers expected to be entirely free from the care of their babies in order to attend to outside duties and pleasures.

The best-known galactogogue is a vigorous nursing infant. It would seem, therefore, that the stimulus of sucking would be increased as the weight of the infant increases. Some relationship has been found to exist between the demands[1, 17, 18] and the weight at birth[6, 19-21] of the infant and the amount of breast milk secreted.

In this study we used the records of 462 mothers who were delivered of full-term normal babies and whose duration of breast feeding was known. All of them, after delivery, expressed the desire to feed their infants at the breast.

*Fellow in Pediatrics, Mayo Foundation, Rochester.

The mothers varied in age from 16 to 43 years, and the mean age was 27.8 ± 0.26 years. The infants of 40.3 per cent of the women were their first living children; 59.7 per cent of the mothers had two or more living children. Of this group, 27.8 per cent of the women lived on farms and 72.2 per cent lived in towns or cities.

The adequacy of the supply of breast milk can be considered at two different periods: (1) when the mother is dismissed from the hospital on the ninth day (mean value), and (2) when the mother ceases to nurse entirely. When these mothers went home with their new infants, 69.0 per cent of the babies were fed breast milk exclusively, 14.9 per cent received complementary feedings and 16.1 per cent were fed by the nursing bottle alone. The average duration of breast feeding for the entire group was 2.8 ± 0.19 months.

At the time of dismissal of the mothers and children from the hospital, the adequacy of the supply of breast milk was not affected by the factor of age until after those mothers were encountered who had reached the age of 30 years, as is shown in Fig. 1. For those mothers in this older age group, there was a significant increase in the inadequacy of breast feeding as compared to those mothers less than 30 years of age. Most of the mothers more than 30 years old who had an inadequate supply of breast milk were delivered of their first living child. There was an increase of 21.4 per cent in inadequacy of breast milk among those women more than 30 years old who were delivered of their first living child as compared to the younger mothers; there was an increase of 12.9 per cent in inadequacy of breast milk for those more than 30 years of age who had more than one living child, as compared to the younger women.

However, in respect to duration of breast feeding, the mothers more than 30 years of age breast fed their babies as many months (mean value 2.8 ± 0.24 months) as did those mothers who were younger (mean value 2.8 ± 0.17 months).

On dismissal from the hospital, 32.3 per cent of those mothers with one living child had an inadequate supply of milk as compared with inadequacy of supply among 29.0 per cent of those who had more than one child. Since the duration of breast feeding was equal for each group, it can be said that the number of living children a mother has does not significantly affect the supply of breast milk either while the mother is in the hospital or after she has been dismissed.

On dismissal from the hospital, 20.4 per cent of the farm women were unable to breast feed their infants, as compared with 32.1 per cent of urban women who were not able to nurse their children. The farm women breast fed their infants (mean value, 3.36 ± 0.30 months) for a significantly longer period than did those mothers who lived in towns (mean value, 2.56 ± 0.16 months).

ENGORGEMENT

At least once daily the mothers' breasts were gently palpated to determine the day of onset of lactation and the degree of engorgement. The day that engorgement of the breasts began did influence the supply of milk available on dismissal of the mother from the hospital, as is shown in Table I, in which a progressive decrease of the duration of breast feeding is shown as the number of days to the onset of engorgement increases. At the height of engorgement,

if it was present, the degree of engorgement was graded as follows: grade 1, little or no engorgement; grade 2, moderate firmness of the breasts; grade 3, hard, firm breasts that become soft within two to four days; grade 4, hard, firm breasts that do not become soft until after four days. Those women who had engorgement of grade 1 or grade 4, as shown in Table I, had less success in breast feeding their infants than did those who had engorgement of grade 2 and grade 3. Since only eleven women had massive engorgement of grade 4, these data have little statistical significance. However, it is an interesting clinical observation that 72.7 per cent of those mothers (eleven) with prolonged

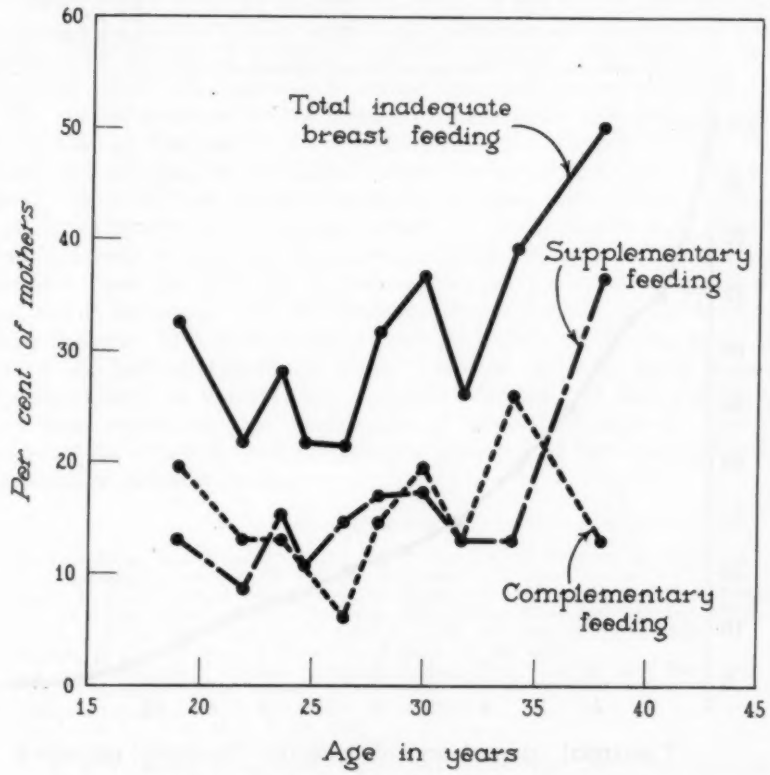


Fig. 1.—Percentage of mothers with inadequate breast feeding.

engorgement of grade 4 had an inadequate supply of breast milk at the time of their dismissal from the hospital. The duration of breast feeding was significantly decreased 1.1 ± 0.31 months among those mothers with engorgement of grade 1 and engorgement of grade 4 as compared to the duration of breast feeding among those whose engorgement was of grade 2 or grade 3. Other maternal factors considered were weight at the onset of pregnancy, height and the weight-length ratio as an index of body build. These factors did not influence the supply of breast milk.

TABLE I. DAY OF ONSET OF ENGORGEMENT AND AMOUNT OF ENGORGEMENT IN RELATION TO SUPPLY OF BREAST MILK

ENGORGEMENT	NUMBER	INADEQUATE SUPPLY OF MILK AT DISMISSAL (PER CENT)	AVERAGE DURATION BREAST FEEDING (MO.)
Day of onset			
2	23	13.0	3.2 ± 0.65
3	254	25.2	3.1 ± 0.18
4	168	39.3	2.4 ± 0.22
5	15	58.8	1.8 ± 0.60
Grade			
1	64	50.0	1.9 ± 0.29
2	317	26.8	3.0 ± 0.15
3	70	25.7	2.7 ± 0.36
4	11	72.7	0.9 ± 0.60

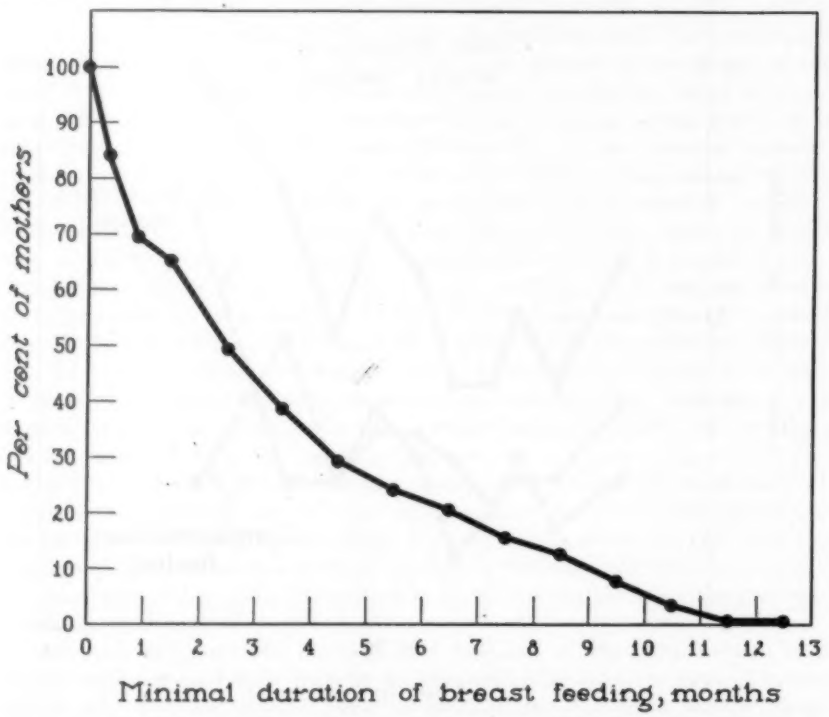


Fig. 2.—Cumulative percentage for mothers' breast feeding for the indicated minimal number of months. The ordinate gives the percentage of all mothers studied who breast fed their infants for any number of months. For instance, 60 per cent of the mothers breast fed their infants for one and three-fourths months or more, 30 per cent breast fed their infants for four and a half months or more.

Weight of the baby at birth did not influence the adequacy of lactation on dismissal of the mother from the hospital. The correlation coefficient between the birth weight of the infant and the duration of breast feeding was — 0.05,* which is not significant.

*The random probability of getting a correlation as large as 0.05 in samples of this size is 0.49; only probability values equal to or less than 0.05 generally are considered to be statistically significant.

Wide variation is encountered in the literature as to the duration of breast feeding. In Fig. 2 is shown the cumulative percentage for mothers who fed their infants at the breast for the indicated number of months or more. It is interesting to note that the sharpest decrease occurs within the first month. Hence, this is the period for physicians to concentrate on, if breast feeding is to be prolonged. Half of the mothers abandoned breast feeding as a source of food for their infants within two and a half months.

SUMMARY AND CONCLUSIONS

The duration of breast feeding in a group of 462 women was investigated in relation to certain factors in both the mothers and their infants. After women reach the age of 30 years, there is a decrease in the adequacy of the supply of breast milk, particularly among those delivered of their first living child. As was evidenced by the number of infants who were being breast fed at the time of dismissal of their mothers from the hospital, the age of the mother did not affect the duration of breast feeding, once it had become established. Parity did not influence the supply of breast milk. Those women who lived in the country breast fed their infants 0.8 months longer than those who lived in a town or city. As the number of days before onset of engorgement increased, there was a decrease in the adequacy of breast feeding, seen both on dismissal of the mother from the hospital and as a decrease in the duration of breast feeding. It is an interesting observation that, on the one hand, those women who had engorgement of grade 1 and, on the other hand, those who had engorgement of grade 4, were less able to breast feed their infants than were those women who had engorgement of grade 2 or grade 3. The birth weight of the infant did not influence the adequacy of the supply of milk or the duration of breast feeding.

REFERENCES

1. De Lee, J. B., and Greenhill, J. P.: The Principles and Practice of Obstetrics, ed. 8, Philadelphia, 1943, W. B. Saunders Company, 1,101 pp.
2. Routh, C. H. F.: Infant Feeding and Its Influence on Life; or the Cause and Prevention of Infant Mortality, ed. 3, New York, 1879, William Wood and Company, 270 pp.
3. Routh, C. H. F.: M. Times & Gaz., Lond. n. s. 18: 467; 494; 520; 573, 1859.
4. Stewart, H. L., and Pratt, J. P.: West. J. Surg. 49: 98, 1941.
5. van Swieten, Gerhard: Quoted by Hamill, S. McC.: Am. J. M. Sc. 125: 1044, 1903.
6. Carlson, Mathilda: Arch. Pediat. 38: 568, 1921.
7. Robinson, Margaret: Arch. Dis. Child. 17: 23, 1942.
8. Hughes, E. L.: Brit. M. J. 2: 69, 1942.
9. Martin, G.: Arch. f. Gynäk. 74: 513, 1905.
10. Neale, A. V., Cassie, Ethel, Braid, Frances and Pierce, Mila: Arch. Dis. Child. 18: 59, 1943.
11. Hamilton, C. K. J.: Practitioner 142: 187, 1939.
12. McNeil, Charles: Practitioner 150: 193, 1943.
13. Grulee, C. G.: Proc. Inter-State Postgrad. M. A. North America (1943), 1944, pp. 135-137.
14. Worcester, A.: Boston M. & S. J. 143: 361, 1900.
15. Richardson, F. H.: Hygeia 20: 224, 1942.
16. Darner, C. B., and Hunter, G. W.: Am. J. Obst. & Gynec. 45: 117, 1943.
17. Moore, C. U.: Arch. Pediat. 36: 609, 1919.
18. Sedgwick, J. P.: Am. J. Dis. Child. 21: 455, 1921.
19. Gedda, E.: Nord. hyg. tidskr. 21: 185, 1940.
20. Wardlaw, H. S. H., and Dart, E. E. P.: M. J. Australia 2: 377, 1934.
21. Wardlaw, H. S. H., and Dart, E. E. P.: M. J. Australia 2: 564, 1932.

PORTAL CIRRHOSIS OF THE LIVER

Case Report With Discussion of Problems

Walter M. Block, M.D.
Cedar Rapids, Iowa

A CASE of hepatic cirrhosis in a boy 11 years of age is presented, because it is felt that any information is worth while which may throw some light on a relatively uncommon disease whose cause is still unknown.

In this institution, only three proved cases of primary liver cirrhosis in children occurred during the past twenty years. One was that of a boy 7 weeks old, and two were those of girls, 2 and 6 years old, respectively. Three other patients were clinically suspected of having had the disease, but died outside of this hospital and autopsy was not performed. "Cardiac" cirrhosis, due to chronic, passive congestion of the liver was seen in four children with primary heart disease (Table I).

Further statistics concerning the frequency of cirrhosis in children are cited by Moon.[1]

CASE REPORT

R. J., an 11-year-old white boy, was admitted to the Children's Hospital on Nov. 5, 1946, with entrance complaints of abdominal swelling for three weeks and jaundice for four weeks.

The patient's past history was not contributory. The mother's pregnancy was uncomplicated, the delivery was normal, the birth weight was 10 pounds. The child was bottle fed, made normal development, and had never been seriously ill. He had measles, pertussis, chicken pox, and an episode of "strep throat," all without complications. The family history revealed that he was the son of a minister, that there were six siblings, two of whom had died (a boy, aged 24 years, of encephalitis, and a boy, aged 3 years, of pneumonia). There was no history of any familial or liver diseases, syphilis, or tuberculosis in the family.

The patient's present illness began in September, 1946, when he complained of loss of appetite. Prior to September he had been in perfect health. Loss of "pep" was then noticed by the boy's parents, as well as fever of 101° F. orally. Nausea and a few episodes of vomiting were the subsequent complaints. Jaundice, together with dark urine and clay-colored stools were noticed about October 10. At that time a physician saw the patient and diagnosed "virus hepatitis." Soon thereafter, "swelling" of the abdomen developed; the jaundice decreased, the stools regained normal color, but the abdominal swelling increased. Toward the end of October he was taken to a hospital where paracentesis yielded 3 L. of lemon-yellow fluid. The illness became progressively more severe. The boy began to complain of weakness and pain in the knees, and later also in the ankles and wrists. He became dyspneic and was brought to this clinic.

Physical examination revealed a well-developed, very well-nourished, husky looking boy who appeared acutely ill and was in obvious respiratory distress. There was an icteric tint to the sclerae, marked distention of the abdomen, and dilatation of the superficial chest and abdominal veins. Other positive findings consisted of hypertrophic tonsils, dullness to percussion with diminished breath sounds over the lower, left, posterior, and lateral chest wall. The heart presented no unusual findings and the blood pressure was 140/70.

The peritoneal cavity appeared to be filled with fluid. There was a healing paracentesis wound just below the umbilicus. The liver was felt 8 cm. below the right costal

From the Department of Pediatrics, College of Medicine, State University of Iowa.

TABLE I. CASES OF JUVENILE CIRRHOSIS OBSERVED DURING THE PAST TWENTY YEARS AT THE CHILDREN'S HOSPITAL

Diagnosis established by necropsy	1. Girl, 14 years; "Banti's" disease and portal cirrhosis 2. Boy, 7 weeks; periportal cirrhosis. No obstruction of bile ducts found 3. Girl, 6 years; portal cirrhosis with typical "hob-nail" liver
Diagnosis clinically suspected	1. Girl, 11 years; ulcerative colitis; chronic nephritis; probable cirrhosis of the liver. Died two years after last seen 2. Boy, 4 years; possible liver cirrhosis. Died several months after last seen, with much ascites 3. Girl, 11 years; splenohepatomegaly; Banti's disease or primary liver cirrhosis. Died several months after last seen
"Cardiac" cirrhosis. Diagnosis established by: 1) Necropsy Cases 1, 2, 3 2) Surgical exploration Case 4	1. Girl, 13 years; adhesive pericarditis; perisplenitis; ascites and mild cirrhosis of the liver 2. Girl, 4 years; rheumatic carditis; chronic, passive congestion of liver and spleen with ascites 3. Girl, 11 years; rheumatic fever; verrucose endocarditis; chronic, passive congestion of liver and spleen 4. Girl, 16 years; adhesive pericarditis; chronic, passive congestion of liver with signs of cirrhosis. Diagnosis established during surgery (cardiolysis); patient living and well

margin, was firm, and very tender to palpation. The spleen could not be felt. There was mild, pitting edema of the lower legs.

Report of X-ray Examination of the Chest.—(Dr. C. L. Gillies.) "A single film of the chest taken with the patient upright shows both leaves of the diaphragm to be elevated. There is no fluid in the left pleural cavity. The heart does not appear to be enlarged. The lung fields are clear. Fluoroscopically, excursions could be observed along the left border of the heart which appeared to be of normal amplitude."

Laboratory Studies.—Five urine examinations revealed satisfactory concentration, a trace of sugar in two of the specimens, and a trace of albumin in the last one specimen, which also contained a few, finely granular casts. Microscopic examination of the urine was otherwise negative. Blood studies showed the hemoglobin to be 11.35 Gm. per 100 c.c. (Newcomber method), a red cell count of 3,470,000, and three white cell counts varying between 10,000 and 12,250 cells per cubic millimeter. The differential count showed 1 per cent basophiles, 2 per cent eosinophiles, 12 per cent stab cells, 61 per cent segmented polymorphonuclear cells, 22 per cent lymphocytes, and 2 per cent monocytes. The polymorphonuclear cells showed marked, toxic granulation. The platelet count was 68,000 prior to splenectomy, and 92,000 one day postoperatively. The reticulocyte count was 5.3 per cent and 4.3 per cent on the first postoperative day. Other blood studies showed the following values: hematocrit, 32 per cent; bleeding time, 6 minutes; coagulation time, 7 minutes; and prothrombin time, 2 minutes, 26 seconds (Control: 41.1 seconds). Fragility test of the erythrocytes showed hemolysis to begin at 0.42 per cent of saline solution and to be complete at 0.35 per cent.

Chemical studies of the blood revealed the following values per 100 c.c.: serum bilirubin, 6.5 mg. (post mortem, 25.6 mg.); cholesterol, 151 mg.; cholesterol esters, 58.5 mg. or 38.5 per cent of total cholesterol; nonprotein nitrogen, 27.2 mg.; total proteins, 6.6 Gm.; albumin, 1.4 Gm.; globulin, 5.0 Gm.; fibrinogen, 0.2 Gm.; van den Bergh reaction, prompt direct.

Serologic reactions of the blood showed Kahn, Kline, Kolmer tests to be 4 plus positive (post mortem, Kahn test 3 plus positive, Kline and Kolmer tests, negative). Heterophile antibody test (post mortem), negative. Examination of the stools showed two specimens negative for ova, parasites, or cysts. Culture of stool was negative for Eberthella, Salmonella and Shigella groups.

Examination of ascitic fluid showed a yellowish color; the specific gravity was 1.0145; nonprotein nitrogen, 27 mg. per 100 c.c. of fluid; proteins, 0.444 Gm. per 100 c.c. of fluid; culture revealed *Escherichia coli*. Culture of pleural fluid revealed the same organism. One blood culture was negative.

A working diagnosis of inflammatory liver disease was made. During his short hospitalization, the patient's temperature fluctuated between 102° and 103° F. rectally. The lowest readings were 100.2° F. on two occasions. The pulse rate followed the temperature curve. Preoperatively, the respiratory rate averaged 40 to 44 per minute.

Treatment was symptomatic at first, but penicillin in large doses, intramuscularly as well as intravenously, was soon administered. November 7, the third hospital day, the patient's condition was markedly impaired. He appeared very toxic, three emeses of "coffee-ground"-like material occurred, and the patient, mentally confused, had a mild, clonic convulsion. The blood pressure was 137/80 at that time. An exploratory laparatomy was decided on and was performed November 9. On opening the abdomen, 2,500 c.c. of straw-colored fluid escaped from the peritoneal cavity. The liver looked yellowish in color, and was of nodular, "hob-nail" character. The spleen was found to be two to three times its normal size. A biopsy of the liver was done, and splenectomy as well as omentopexy was performed. These were carried out because there was little else to offer this patient and it was thought that the latter two procedures might be instrumental in lightening the venous blood flow through the portal veins. The immediate postoperative condition of the patient was fairly good. However, he expired in the morning of the second postoperative day.

NECROPSY REPORT* (ABSTRACT)

Necropsy revealed severe portal cirrhosis with jaundice and ascites. Four thousand cubic centimeters of yellow, bile-tinged, moderately foul smelling fluid were removed from the peritoneal cavity. The liver weighed 1,250 Gm., was essentially normal in contour, but showed a generalized, severe, hob-nail type of cirrhosis (Fig. 1). The capsule of the liver was thickened and fibrotic and the liver parenchyma consisted of pinhead-sized to pea-sized masses of deeply stained, yellowish green, regenerated liver lobules (Fig. 2). It cut with considerable resistance. The normal architecture of the liver was considerably deranged by the multiple nodules previously mentioned. There was no gross evidence of hemorrhage, necrosis, or fatty replacement in the liver, and no abscess was found.

Sections showed many lobules of liver cells widely separated and walled off by considerable dense fibrous tissue in which there were numerous proliferating bile ducts and scattered groups of hepatic cells and ductal epithelium (Fig. 3). There was no lobular orientation in the groups of liver cells. Most of the cells were large and irregular and contained many vacuoles and yellowish brown granules in the cytoplasm. The nuclei of many appeared normal but in others the nuclei were seen to be large and very vesicular and in many no nucleus was seen at all. There was extensive degeneration of the liver cells of the proliferating, regenerating nodules (Fig. 4). The fibrous tissue was seen to be moderately and diffusely infiltrated with lymphocytes. A few small areas of focal hemorrhage were present also. Mallory's aniline blue stain of a section of liver confirmed the presence of increased amounts of fibrous connective tissue about the irregular liver lobules. Sudan III fat stain showed many small droplets of free fat present in the liver cells. Levaditi stain of the liver failed to reveal any *Treponema pallidum*.

The spleen weighed 340 Gm. There was moderate congestion of back-pressure type. Microscopic sections revealed increase in the fibrous tissue of the pulp, dilated sinuses, and small Malpighian corpuscles. There were no siderotic nodules, and no more pathologic changes than expected with hepatic cirrhosis (Fig. 5).

The lungs were congested and edematous and showed many areas of atelectasis, violent, necrotizing pneumonia, and focal, interstitial hemorrhages. The heart was marked by petechiae, somewhat hypertrophied, and dilated and flabby.

Incidental findings included edema and low-grade inflammation of the colon; petechiae of the stomach, small bowel, and colon; an infected and necrotic leiomyoma of the cecum; hyperplasia of the bone marrow; and atrophy of the testes and gynecomastia. Microscopic sections of the breast tissue (Fig. 6) showed marked proliferation of the ducts, lined by a hyperplastic epithelium and surrounded by a light, vascular, fibrous, tissue stroma.

*Acknowledgment is made to Dr. E. D. Warner, head of the Department of Pathology, for interpretation of the reproductions.

The cause of death was the extensive destruction of functional liver tissue with its resultant, widespread, systemic effects. The changes in the lungs can be considered terminal events, secondary to the liver disease, but contributing factors in the death of the patient. The impression gained was that of a very active (as indicated by the extensive necrosis within the nodules of regenerating liver tissue) and virulent hepatitis, leading to cirrhosis.

Fig. 1.

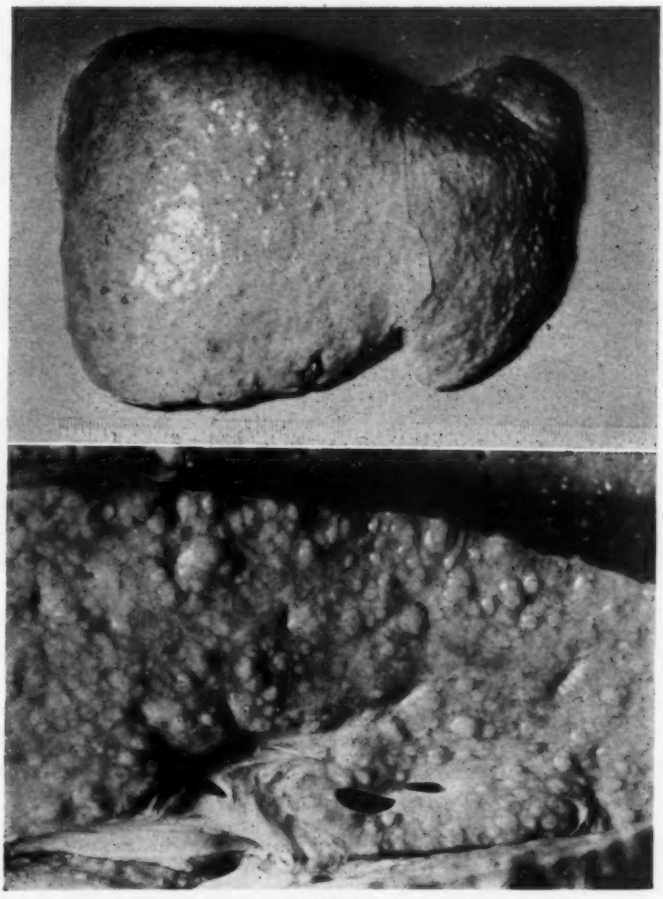


Fig. 2.

Fig. 1.—Gross appearance of liver.
Fig. 2.—Gross appearance of capsular and cut surfaces of liver.

COMMENT

Terminology.—The classification and terminology of the various types of liver cirrhosis are still far from being satisfactory. Complaints are many that the present terminology is more confusing than helpful (Moon,[1] Levy,[2] Evans[3]).

Until more is known about the cause of this disease, it appears that the simple, conventional classification into three groups, namely, syphilitic, portal, and biliary cirrhosis, is satisfactory for pediatric use, since it at least prevents

Fig. 3.

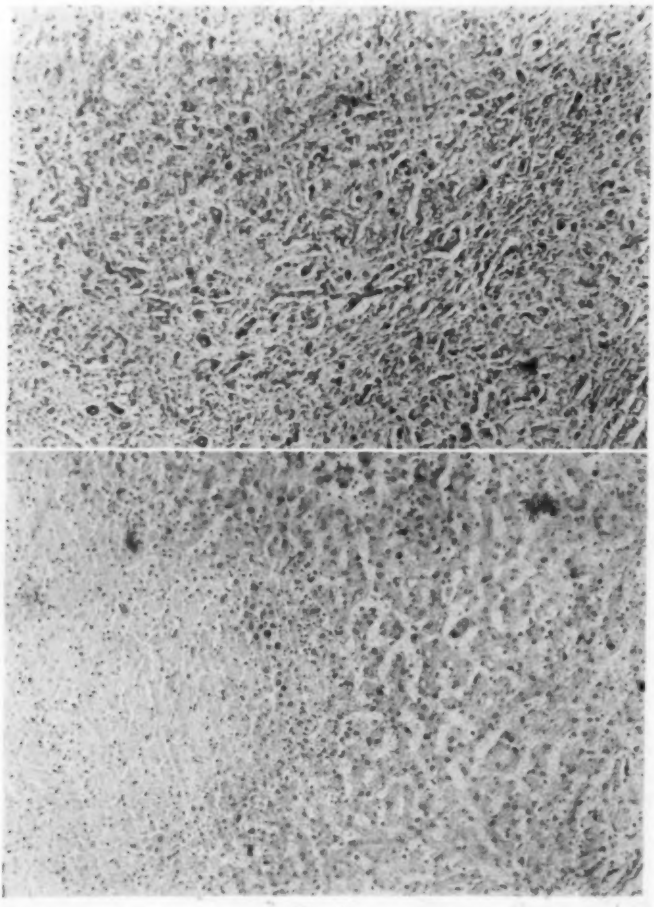


Fig. 4.

Fig. 3.—Numerous proliferative bile ducts in scar tissue between nodules of hepatic cells.
Fig. 4.—Necrosis in nodule of hepatic cells.

misunderstandings. With due respect to many scientists, the complicating use of surnames should be abolished, in the case of this as well as most other diseases, thus eliminating the question of what constitutes true "Laennec's" cirrhosis, or which form of biliary cirrhosis, if any, can rightfully be called "Hanot's" cirrhosis.

Pathologic descriptions should not be included in the terminology, but should be reserved for the pathologist to elaborate on in his report. This in-

cludes expressions like "hypertrophic" (for biliary) cirrhosis, or "atrophic" (for portal) cirrhosis, unsuitable for pediatric use, since, due to the notoriously fast course of the disease in children, many will die before the liver has had time to become atrophic. Actually, at necropsy, the liver will frequently be found to be hypertrophic in cases of so-called "atrophic," that is, portal cirrhosis, because of marked parenchymatous regeneration.

Etiologic designations, as for instance "alcoholic" (an unfortunate synonym for portal) cirrhosis should not enter into the terminology, until the cause of the disease is known.

Fig. 5.—Gross appearance of capsular and cut surfaces of spleen.

Pathogenesis.—Recent studies have shown that nutrition may play an important part in the production of cirrhosis. In the case of this very well-nourished boy, we feel sure that dietary insufficiencies were not responsible for his disease.

Infection has been widely discussed as one of the most important causes of cirrhosis. This may be either of spirochetal, bacterial, or virus type.

Cirrhosis due to congenital syphilis could be ruled out in this case. Although positive during life, the Kolmer test was negative with post-mortem blood. There was no history of any syphilitic symptoms, no syphilitic stigmata were found, and all members of the patient's family (parents and siblings) showed negative serologic reactions for syphilis.

The histologic picture of liver sections was not that found in cases of syphilis. Furthermore, cirrhosis due to congenital syphilis would be a most unusual occurrence in an 11-year-old child.

Bacterial infections have been described among others by Moon,[4] who, in 1927, reported two cases of cirrhosis (that of a girl 12 years old and of a boy 14 years old) in whom streptococci were demonstrated in the liver and

spleen. The organisms cultivated from the liver of the boy showed a definite tendency to infect the livers of experimental animals (rabbits). Moon postulates, therefore, that "chronic infection of the liver should be regarded among the important causes of cirrhosis." More recently, Harrell and McBryde,[5] in an instructive review of the subject of juvenile cirrhosis, reported twenty cases of this illness, among them one of a 16-year-old girl whose acute cirrhosis they believed to be due to "infection of the peritoneum, and probably of the liver, with an atypical species of Escherichia."

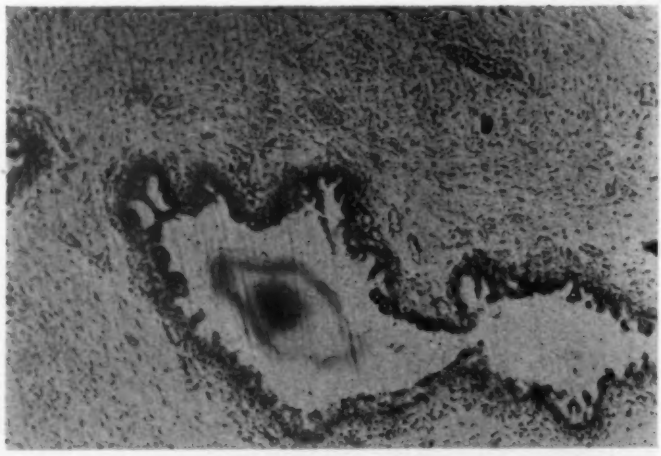


Fig. 6.—Section of breast tissue, showing proliferation of ductal epithelium and periductal stroma.

The fact that colon bacilli were cultured from the ascitic as well as pleural fluid in our case, makes one think of the possibility of an infectious cause of the boy's cirrhosis. However, there is no proof that such was the case.

It may be worth while recalling that liver cirrhosis has been mentioned in the literature as a sequel of acute infectious diseases, among them scarlet fever, enteritis, endocarditis, and others (Seitz, Bingel, and Bolton, as mentioned by Moon[4]). However, the evaluation of some reports should be made with care, since instances of cirrhosis due to "infection" of unspecified nature (Laurie,[6] and Calvin and Saffro[7]) may well have been the end stages of what now is known as infectious hepatitis.

As yet proof is scarce that fatal cases of infectious hepatitis may terminate in cirrhosis. In fact, Lucke[8] emphasizes that the histologic picture in these cases is invariably that of "idiopathic yellow atrophy," and not that of scarring. His interpretations, however, have not been universally accepted.

It is very tempting to assume that some instances of juvenile cirrhosis, fitting like this case into the pathologic picture of "toxic cirrhosis" as described by Mallory, may have been caused by what formerly was termed catarrhal jaundice and has been found to be a virus infection of the liver.

In our case, such an assumption is not without grounds, for acute necrosis, demonstrable even in newly regenerated liver cells, was taking place up to the time of death, indicating an active process. The early symptoms and clinical course of this patient also would well fit the picture of infectious hepatitis. The final answer to the question whether portal cirrhosis can be caused by infectious hepatitis, must of course, come from pathologists. One authoritative statement supporting this assumption has very recently been made by Mallory,[9] who stated, "I feel certain I have seen cirrhosis that could be traced back to hepatitis." Another convincing study is that of two Danish workers, Krarup and Roholm,[10] who reported on pathologic specimens obtained by aspiration biopsies of the livers of twelve patients with "acute or epidemic hepatitis." They demonstrated, by histologic examination, "all sorts of transitions" between acute hepatitis and fully developed cirrhosis and postulate a "nosological unity" of acute hepatitis and cirrhosis of the liver.

Familial Incidence.—This was demonstrated by a number of authors, among them Weber,[11] who has an interesting concept of this familial tendency to develop cirrhosis. He explains familial hepatic cirrhosis as an inborn, constitutional defect in the hepatic cells which diminishes their power of resistance to toxins or causes them to decay prematurely. To this defect, he gave the name of "dysbiotrophy" of tissue, and classified the disease under the "congenital-developmental class of diseases," a group in which he includes such diseases as hemophilia, familial hemolytic icterus, lipodystrophies, glycogen storage disease, and others, including allergic peculiarities.

More recently, Bridgeman[12] and Yater[13] reported instances of familial cirrhosis. In our case, no familial tendency could be demonstrated. Laboratory tests were performed with the blood of the patient's parents and siblings, but no indication of liver disease was found (Table II).

TABLE II. SEROLOGIC REACTIONS AND LIVER FUNCTION TESTS ON PARENTS AND THREE SIBLINGS OF PATIENT

	KOLMER TEST	ICTERIC INDEX	CEPHALIN FLOCCULATION TEST	SERUM PROTEINS (GM. PER 100 C.C.)		
				TOTAL	ALBUMIN	GLOBULIN
Father, 53 years	Neg.	4	Neg.	6.5	3.5	3.0
Mother, 47 years	Neg.	6	Neg.	6.9	3.4	3.5
Brother, 27 years	Neg.	–	–	6.6	3.8	2.8
Brother, 23 years	Neg.	3	Neg.	6.2	4.1	2.1
Sister, 16 years	Neg.	2	Neg.	6.1	3.4	2.7
Sister, 15 years	Neg.	2	Neg.	6.6	3.8	2.8

Diagnosis.—Preoperatively, this patient presented some interesting diagnostic problems.

The fast course of the illness, the presence of fever, and pleural effusion, may make one not familiar with this rather uncommon condition in children think first of possibilities other than liver cirrhosis.

Adhesive pericarditis with cirrhosis and polyserositis was considered in this case, but could be excluded by the absence of any history of previous cardiac difficulties as well as by the negative roentgenologic report.

Infectious mononucleosis can produce clinical pictures similar to this one, with jaundice, enlargement of the liver, fever, falsely positive Wassermann reaction, and even involvement of the central nervous system (Vaughan and associates[14]). However, a study of the white blood cells did not support such a diagnosis. The Paul-Bunnell test performed with post-mortem blood, was negative.

Liver disease due to chemical toxins (as phosphorus, arsenicals) could be ruled out by absence of a history of contact with any such chemicals. Thyrotoxic effects on the liver, leading to cirrhosis (Moon,[15] Barker[16]) were certainly not active, as there were no symptoms or signs of thyroid disease in the case of this boy.

Early in his history, however, there were complaints of abdominal distress, nausea, and vomiting, and fever of 101-102° F. These symptoms could very well be interpreted as signs of appendicitis. It was thought that the patient's present illness may possibly have been a subphrenic, or even a liver abscess, due to such a previous attack of appendicitis. It was mainly because of this consideration, as well as a likelihood of certain death otherwise, that surgery was performed.

Finally, a diagnosis strongly to be considered was that of so-called "Banti's disease." Much controversy has been going on about this disease, and a review of the literature reveals a general tendency, especially on the part of pathologists, with Moon[1] in America and Rössle[17] in Germany as their main advocates, to abandon the expression "Banti's disease." Moon objects strongly to the acceptance of Banti's disease as a separate entity, since it is "clinically and pathologically indistinguishable from atrophic cirrhosis." He suggests the name of "hepatosplenic disease" as more adequate. This represents the English equivalent to the well-known German expression of "Hepatolienale Erkrankungen" (Eppinger). Barker[16] also "confesses," as he puts it, that he too is "very doubtful of the unitary existence of any malady that is responsible for the whole group of cases described in the bibliography as "Banti's disease." He states that many of the cases described as Banti's disease, turned out to be instances of chronic pylephlebitis, and atrophic cirrhosis of the liver with stasis in the spleen.

Poynton and Wyllie[18] claim that absence of leucocytosis, a low hemoglobin, and gastrointestinal hemorrhages help to recognize Banti's disease. All three of these findings, however, may be present in primary liver cirrhosis also.

Langmead[19] finds the diagnosis of "splenic anemia" (i.e., Banti's disease) justified in those cases in which the splenomegaly is believed to have preceded the enlargement of the liver and in which there is considerable anemia. However, newer studies have shown that even in primary liver cirrhosis, splenomegaly may occur before enlargement of the liver can be found.

Perhaps a compromise may be acceptable by recognizing a separate clinical syndrome of splenomegaly with anemia, with or without leucopenia, with intermittent fever and hemorrhages from mucous surfaces, in which surgical exploration with biopsy of liver tissue fails to reveal any liver abnormality.

These patients are benefited by splenectomy, and for them the term *splenomegalic anemia,* in preference to "Banti's disease," might be clinically helpful.

Without surgical exploration it is generally impossible to differentiate the two diagnoses, as this patient again demonstrates. That the spleen was not palpable in this case may have been due to the presence of marked ascites, since actually the spleen was found to have been considerably enlarged. The fast course of the disease would speak against the so-called "third stage of Banti's disease" although it might be argued that the boy may have had an enlarged spleen long before the onset of subjective symptoms.

In retrospect, the symptoms and signs in this case were fairly typical for juvenile cirrhosis, including the originally somewhat baffling occurrence of fever, pleural effusion, and the fast course of illness. All three findings have been mentioned frequently in the literature on this subject. (Moon,[1] Curtiss,[20] Kelly,[21] Asselstine,[22] Ratnoff.[23])

Laboratory Findings.—Analysis of the laboratory studies revealed that they were compatible with a diagnosis of severe liver damage. Occasional traces of sugar in the urine are not infrequently found in patients with liver disease. Mild leucocytosis is the usual finding in cirrhosis of the liver. Prolonged prothrombin time also pointed to liver damage. The thrombocytopenia may be interpreted as toxic depression of the bone marrow, although there was a vigorous attempt at blood cell regeneration, as indicated by the relatively high reticulocyte count of 5.3 per cent.

Since the liver is the main site of esterification of cholesterol, the low value obtained for cholesterol-esters also indicated liver damage, as did the serum albumin value of 1.4 Gm. per cent.

The finding of *E. coli* in the fluid obtained from the peritoneal cavity is not fully understood, although the presence of this organism in the sections of the leiomyoma found on the cecum, may be an explanation.

The serologic tests performed on the patient's family were done because of the very unusual reactions obtained with the patient's blood. As stated in the case history, the boy's Kolmer, Kline, and Kahn tests all gave 4 plus positive reactions during life, while Kolmer and Kline tests gave negative reactions with post-mortem blood. This is the more surprising since bilirubinemia, which may explain falsely positive reactions, was more pronounced post mortem (25.6 mg. per cent) than during life (6.5 mg. per cent). Although the number of pathologic conditions in which falsely positive serologic reactions can be obtained is rising constantly, a 4 plus positive reaction with all three tests is rather unusual. We are at a loss to explain this finding.

Finally, an observation is worth mentioning which would add another case to the number of patients with liver cirrhosis in whom disturbances of the endocrine system have been found. Zondek advanced the theory that the liver inactivates sex hormones and there is ample experimental proof of that. Glass and co-workers[24] studied fourteen male patients with cirrhosis and found gynecomastia in eight of them and testicular atrophy in all of them. Assay of urine specimens for androgens and estrogens revealed low values for the former, but the presence of practically all of the estrogens in free form. These

authors concluded that gynecomastia and atrophy of the testes are striking concomitants in the majority of cases of liver cirrhosis. Physical examination and pathologic studies revealed that in the case of this boy also, gynecomastia and testicular atrophy were present.

SUMMARY

1. A case of portal cirrhosis in an 11-year-old boy is presented, together with the pathologic findings observed during necropsy.

2. The terminology and pathogenesis are reviewed, as well as the differential diagnosis, especially in regard to "splenomegalic anemia."

3. The thought is advanced that infectious hepatitis may terminate in cirrhosis.

REFERENCES

1. Moon, V. H.: Am. J. Dis. Child. 46: 375, 1933.
2. Levy, W., Greenstein, N. M., and Leighton, B.: J. PEDIAT. 15: 91, 1939.
3. Evans, P. R.: Arch. Dis. Child. 14: 89, 1939.
4. Moon, V. H.: Am. J. M. Sc. 177: 681, 1929.
5. Harrell, G. T., and McBryde, A.: Am. J. Dis. Child. 59: 1301, 1940.
6. Laurie, N. S.: M. J. Australia 1: 178, 1935.
7. Calvin, J. K., and Saffro, L. B.: Am. J. Dis. Child. 43: 914, 1932.
8. Lucke, B.: Am. J. Pathol. 20: 471, 1944.
9. Mallory, T. B.: Am. Practit. 1: 323, 1947.
10. Krarup, N. B., and Roholm, K.: Acta Med. Scand. 108: 306, 1941.
11. Weber, F. P.: The Lancet 1: 365, 1936.
12. Bridgeman, M. L., and Robertson, T. D.: Am. J. Dis. Child. 43: 1153, 1932.
13. Yater, W. M.: Med. Ann. Distr. Columbia 12: 264, 1943.
14. Vaughan, S. L., Regan, J. S., and Terplan, K.: Blood 1: 4, 1946.
15. Moon, V. H.: Arch. Path. 18: 381, 1934.
16. Barker, L. F.: Med. Clin. N. Am. 14: 99, 1930.
17. Rössle, R. in Henke, F., and Lubarsch, O.: Handbuch der spez. Anat. und Histol., Bd. 5, 1. Teil, Berlin, 1930, J. Springer, page 278.
18. Poynton, F. J., and Wyllie, W. G.: Arch. Dis. Childh. 1: 1, 1926.
19. Langmead, F.: Proc. Roy. Soc. Med. 27: 939, 1924.
20. Curtiss, C. C.: Arch. Pediat. 51: 396, 1934.
21. Kelly, A. D.: Am. J. Dis. Child. 51: 480, 1936.
22. Asselestine, St. M.: J. Canad. M. A. 24: 545, 1931.
23. Ratnoff, O. D., and Patek, A. J., Jr.: Medicine 21: 207, 1942.
24. Glass, S. J., Edmondson, H. A., Soll, S. N.: Endocrinol. 27: 749, 1940.

DENTAL CARIES EXPERIENCE IN POSTWAR ITALY (1945)

II. Among Teen-Age Children in Naples

Maury Massler, D.D.S., M.S.,* and Isaac Schour, D.D.S., Ph.D.†
Chicago, Ill.

INTRODUCTION

FOLLOWING an extensive study of the prevalence of dental decay in four cities of postwar Italy (Schour and Massler, 1947), a more intensive dental study was made of 162 Neapolitan children 10 to 18 years of age. These children showed decided retardation in both growth (understature and undergroup studied in Naples, and they were subjected to a more detailed medical and dental investigation.

Nutritional Status of Teen-Age Neapolitan Children in 1945.—These children were selected on the basis of their age alone from the more general age weight) and development (menarche); pallor, fatigue, and clinical signs of some specific nutritional deficiencies, particularly vitamin A and vitamin B complex (thiamin, riboflavin and niacin) (Kyhos). The food intake was low in quantity and deficient in quality, approximately 50 per cent of the required proteins and calories being available (Flumerfelt).

METHOD OF EXAMINATION

Examination of the oral cavity was made with special care, in a dental chair, using a mouth mirror and explorer under excellent lighting conditions. All teeth were recorded by a well-trained assistant.

Carious surfaces were noted as well as restorations and missing teeth.

Caries Prevalence, Decayed, Missing, or Filled (DMF) Teeth per Person.—Caries experience was recorded by summing up the total number of permanent teeth which were decayed (D), missing because of caries (M), or filled (F). Since extractions and fillings were rarely observed in this group, the caries experience is concerned almost entirely with decayed teeth.

In contrast to the extensive survey, where only the number of DMF teeth per person was computed, additional criteria for the assessment of dental decay were used in this study, since there are a number of limitations to an analysis of dental decay which is confined simply to counting the number of decayed teeth. Such a number does not give a complete picture of the carious processes. It disregards the site and extent of the lesion and the tooth affected. It may even be misleading, since an equal weight is given to a carious cavity in the first permanent molar, which is very commonly affected by decay, and to a

*Associate Professor of Pedodontics, University of Illinois College of Dentistry.
†Professor and Head of Department of Histology, University of Illinois College of Dentistry.

This study was conducted under the auspices of the Italian Medical Nutrition Mission. Grateful acknowledgment is given to the Unitarian Service Committee, the Congregational-Christian Service Committee and the UNRRA for providing the necessary facilities for this investigation.

This paper is the second in a series dealing with the prevalence of dental caries in subnutrition and malnutrition groups in postwar Italy.

carious cavity in the lower incisor, which is very rarely affected. Yet the presence of decay in a lower permanent incisor is far more significant than its occurrence in a first permanent molar.

Similarly, the site of the initial lesion in terms of the topography of a given tooth is important, since the sites of predilection are pits and fissures and contact areas, in that order. Cervical decay is much less common, while decay of the smooth middle third of the labial or lingual surfaces is extremely rare. The following data was therefore obtained in addition to counting the number of DMF teeth:

1. Number of surfaces per tooth attacked by caries.
2. Ratio of the number of carious surfaces to the number of carious teeth per person.
3. Location of the lesion.
4. Degree of caries.
5. Prevalence of decay in first permanent molars.

*Number of DMF Tooth Surfaces Attacked by Caries per Person.**—The number of carious tooth surfaces per child was computed by dividing the total number of carious surfaces by the number of children observed. Although each tooth has five surfaces, a completely carious crown (or extracted tooth) was given a value of three carious surfaces, as suggested by Bodecker (1939). This is valid, since the character of the site of injury is more important than the anatomic location of the surface attacked. In our study, we considered decay as beginning in pits and fissures rather than occlusal decay, proximal (contact area) rather than mesial or distal decay, and cervical decay rather than labial (buccal) or lingual surface decay (Table I). Clinical observations confirmed the desirability of this type of analysis rather than the more commonly used surface designation, although in most cases the two systems are quite similar.

TABLE I. ANALYSIS OF DENTAL CARIES IN 162 NEAPOLITAN CHILDREN AGES 10 TO 18 YEARS

Caries Experience			
DMF permanent teeth per person		1.67	
DMF permanent tooth surfaces per person		2.45	
Caries Rate			
Number children DMF free (0)		57 (35.0%)	
Number children with caries		105 (65.0%)	
		162 (100%)	
Number children with mild caries	(1+)		88 (83.8%)
Number children with moderate caries	(2+)		16 (15.2%)
Number children with severe caries*	(3+)		1 (1.0%)
			105 (100%)
Caries Topography			
Pit and fissure decay (occlusal)		234 surfaces	(58.8%)
Proximal decay (mesial and distal)		148 surfaces	(37.2%)
Cervical decay (buccal and lingual on enamel)		16 surfaces	(4.0%)
Cemental caries		0 surface	(0.0%)
Total number carious surfaces		398	(100%)

*Severe caries occurred in 46 first permanent molars. These were evaluated as 3 carious surfaces, one pit and fissure and 2 proximal carious surfaces, on the basis of clinical observations.

*Carious tooth surface or tooth surface attacked by caries is defined as one exhibiting active decay, filled, or missing because of caries.

Ratio of Carious Surfaces to Carious Teeth.—This ratio gives some idea of the number of surfaces attacked per carious tooth (Boyd and Cheyne, 1946).

Location of the Lesion.—Each lesion in each tooth was characterized as being pit and fissure decay (occlusal), proximal decay (mesial or distal), cervical decay (buccal or lingual surfaces on enamel) or cemental caries. Buccal pit decay in molars and lingual pit decay in the upper incisors were recorded separately but were uncommon.

Degree of Caries.—An estimation of the degree of decay (mild, moderate, or severe) was made for the entire dentition in each child, taking into consideration the following factors: (a) the class of teeth affected; (b) the extent and depth of the carious cavities; (c) the posteruptive age of the teeth affected.

Mild: Small lesions confined to teeth of highest caries susceptibility (the first and second molars).

Moderate: Extensive and destructive lesions in molars and/or small lesions in teeth of intermediate caries susceptibility (bicuspids and upper incisors).

Severe: Destructive lesions in molars and bicuspids and/or caries present in teeth of least susceptibility (cuspids and lower incisors).

Other things being equal, the degree of caries was considered to be more advanced in proportion to the shorter posteruptive life of the teeth involved. Similarly, while the limitation of caries to the molars would tend to the designation of mild decay, the presence of deep caries and the subsequent destruction of the crown in more than two molars would lead to the designation of moderate. Furthermore, caries was designated as being severe even if only the molars were affected, provided the destruction of the crowns occurred at an early posteruptive age of these teeth, as in a 7-year-old child.

FINDINGS

Number of DMF Teeth and Decayed Surfaces per Person.—Of 162 teenage Neapolitan children, there was an average of 1.67 DMF permanent teeth and 2.45 DMF permanent tooth surfaces (Table I). The ratio of carious surfaces to carious teeth was 1.46 carious surfaces per DMF tooth. This is low in comparison with findings in comparable groups in Hagerstown, Md., where approximately 5.5 DMF permanent teeth and 11.3 decayed permanent tooth surfaces per person or 2.05 DMF surfaces per DMF tooth per person was found (Klein and Palmer, 1941).

Per Cent of Children With No DMF Teeth.—Of the children, 35 per cent were caries-free. This was unusually high, since the average per cent of caries-free children of ages 10 to 18 in Hagerstown was approximately 8.5 per cent, according to Klein and Palmer (1941) (Table II).

Degree of Caries.—When caries did occur (in 65 per cent of the children) it was usually mild (in 83.8 per cent of the children with caries) and did not extend over more than half of the surface of the tooth attacked (Table I). A percentage of 87.4 of all the carious teeth were molar teeth, while 88.6 per cent of all the carious surfaces were confined to the first and second molars (Table III). The extensive and deeply penetrating type of decay which rapidly at-

TABLE II. COMPARISON OF CARIES EXPERIENCE IN 162 CHILDREN 10 TO 18 YEARS OF AGE OF NAPLES, ITALY, AND OF HAGERSTOWN, MD.

CARIES EXPERIENCE	NAPLES	HAGERSTOWN*
Per cent Children caries free	35.0	8.5
Per cent Children with caries	65.0	91.5
DMF permanent teeth per person	1.67	5.5
DMF permanent tooth surfaces per person	2.45	11.3
Ratio of DMF surfaces to DMF teeth	1.46	2.05

*Averages of detailed data presented by Klein and Palmer, 1941.

tacks the entire dentition (including the lower incisors) and which is not uncommon in the United States (Massler, 1945) occurred in this group in only one case.

Sites of Predilection.—As was expected, more than half of the carious lesions began in occlusal pits and fissures and progressed at a slow rate (Table I).

First Permanent Molars.—The first permanent molars, which have the longest exposure to the risk of caries attack in point of time and have the highest susceptibility because of the presence of pits and fissures, are, therefore, most commonly attacked by caries (morbidity) and most frequently lost by extraction (mortality). This tooth also suffered the greatest injury in this group (Table III). The four first molars alone account for 74 per cent of the DMF teeth and 78 per cent of the DMF tooth surfaces (Table III).

TABLE III. DISTRIBUTION OF CARIES IN DIFFERENT CLASSES OF TEETH AMONG 162 NEAPOLITAN CHILDREN (10-18 YEARS OF AGE)

CLASSES OF TEETH	DMF CARIOUS TEETH	DMF CARIOUS SURFACES
Number in:		
Upper incisors	15 (5.6%)	19 (4.7%)
Upper and lower bicuspids	19 (7.0%)	26 (6.5%)
Upper and lower second permanent molars	35 (13.0%)	43 (10.8%)
Upper and lower first permanent molars	201 (74.4%)	310 (77.8%)
Total Number	270 (100 %)	398 (100 %)
Lower first permanent molars	136 (50.4%)	204 (51.2%)
Upper first permanent molars	65 (24.0%)	106 (26.6%)

The two *lower* first permanent molars alone accounted for 50.4 per cent of the DMF teeth and 51.2 per cent of the DMF surfaces, while the upper first permanent molars contributed about half of this amount (24.0 per cent of DMF teeth; 26.6 per cent of DMF surfaces).

The distribution of caries in different classes of permanent teeth in our group was similar to but not identical with that reported by Knutson, Klein and Palmer (1938) and by Klein and Palmer (1938). This is due to the fact that the distribution of caries among the different classes of teeth varies considerably with each year of age and the age groupings in the two studies differ slightly. Our group actually covered eight chronological years.

Of all the first permanent molars, 69 per cent were caries-free; thus, only 31 per cent were attacked by caries (Table IV). Of these, 21.3 per cent were slow, simple decay (confined primarily to occlusal pits and fissures). Only 2.7 per cent showed a moderate amount of decay with large lesions, while 7 per cent of the molars were decayed to a point where practically the entire crown was destroyed.

Since the depth and extent of cavitation increases with time, the post-eruptive age of the tooth carrying the lesion should be taken into consideration (Klein and Palmer, 1941). It was noted that the larger sized lesions and the extensive decay which occurred in 9.7 per cent of the first permanent molars were found only in the older aged children. This would indicate that when caries did attack the tooth it was a slow process and it took a long time for the cavity to increase in extent and depth.

Analysis of the distribution of the sites affected by caries shows a remarkable similarity between the distribution in the first permanent molars and in the mouth as a whole, that is, 60 per cent of all caries begin in pits and fissures, 36 per cent in proximal surfaces and 4 per cent on cervical areas (buccal and lingual). (Compare Tables I and IV.) This is not surprising, since the first permanent molars contributed almost 78 per cent of the total number of DMF surfaces.

Comparison of the caries experience in the first permanent molars of Neapolitan with Hagerstown children re-emphasizes the fact that the number of teeth attacked by caries was much lower and the progress of the lesion was much slower in the Italian children than in 14-year-old Hagerstown girls (Table V). The first permanent molar morbidity and mortality in the Italian children was approximately one-half that of Hagerstown 14-year-old girls. In Hagerstown almost three of the four first permanent molars were carious, while in Naples one and one-quarter of the four molars were affected. In Hagerstown, twenty out of every 100 molars were lost by caries; in Naples, only 7 per cent were missing.

TABLE IV. ANALYSIS OF DENTAL CARIES EXPERIENCE IN FIRST PERMANENT MOLARS IN 162 TEEN-AGE NEAPOLITAN CHILDREN

Total number first permanent molars		648	
No. teeth caries free		447	(69.0%)
No. teeth with caries		201	(31.0%)
Number with mild decay	(1+)	138	(21.3%)
Number with moderate decay	(2+)	17	(2.7%)
Number with severe decay (Extractions Indicated)*	(3+)	46	(7.0%)
Total number first permanent molars		648	(100 %)
Total number surfaces affected by caries		310	
Pit and fissure decay (occlusal)		186	(60.0%)
Proximal decay (mesial and distal)		110	(35.5%)
Cervical decay (buccal and lingual)		14	(4.5%)
Total number carious surfaces*		310	(100 %)

*Evaluated as 3 carious surfaces; 1 pit and fissure, and 2 proximal carious surfaces, on the basis of clinical observations.

TABLE V. COMPARISON OF CARIES PREVALENCE IN FIRST PERMANENT MOLARS IN TEEN-AGE CHILDREN OF NAPLES, ITALY AND HAGERSTOWN, MD.

	NAPLES	HAGERSTOWN*
Total number first permanent molars per person	4.0	4.0
Number first permanent molars caries free (per person)	2.76 (69%)	1.11 (28 %)
Number first permanent molars with caries (per person)	1.24 (31%)	2.89 (72 %)
Mortality of first permanent molars (per person)	0.28 (7%)	0.52 (20.5%)

*From data presented by Knutson, Klein and Palmer (J. A. D. A., 1938) for 14-year-old girls.

DISCUSSION

The teen-age child is characterized by increased nutritional needs and dental defects. In the United States the rate of caries progress is most rapid, and rampant caries finds its highest incidence during this age period (Massler, 1945).

The teen-age children of Naples showed decided retardation in both growth (understature and underweight) and development (menarche), pallor, fatigue, and specific nutritional deficiencies (Kyhos). The food intake was low in quantity and deficient in quality, only 50 per cent of the required protein and calories being available (Flumerfelt). In spite of these factors, the caries experience was very much lower than in teen-age children in the United States. These findings seem to contradict the generally accepted thesis that good nutrition will prevent or arrest the progress of decay.

Caries and Malnutrition.—The relation between malnutrition and a low caries experience has been pointed out in other population groups. There is sufficient evidence to suggest that the incidence of caries is *not* increased in areas of lowered nutrition, subnutrition or even in malnutrition. Friel (1922) examined the children in Vienna after the First World War and found evidence of a low incidence of caries in both the deciduous and permanent dentitions. These children averaged about 14 lb. underweight and were correspondingly understatured. Rickets, anemia, and tuberculosis were very common.

Day (1944) examined the teeth of persons in the Kangra District of Northern India where the diets are deficient in calcium, phosphorus, fat, fat-soluble vitamins and vitamin C. A great percentage of the population suffer from rickets and osteomalacia. He found a remarkably low prevalence of dental decay in these people. Children with clinical rickets showed a caries prevalence of only 1.4 cavities per child. Of women suffering from osteomalacia associated with frequent pregnancies, 36 per cent were caries free. There was an average of only 1.5 cavities per person. In 200 teen-age boys, the caries experience was 1.56 cavities per boy. Day points out that there is almost a complete absence of refined sugar in the diet.

Cady (1946) points out the relatively low incidence of caries in malnourished Dutch children residing in Coventry, England. Reports from England (Oliver, 1946), Norway (Collett, 1946), and other areas where nutritional standards have been lowered during the war years, confirm the finding that caries incidence is lowered. Nearly all reports stress the factor of a lowered refined sugar intake.

Repatriated American prisoners of war from the Far East suffering from malnutrition also show fewer carious teeth than healthy and well-nourished persons (Morgan and associates, 1946).

In this country, Dreizen and associates (1946) and Mann and associates (1947) indicate that the caries prevalence is lower in malnourished patients residing in or near Birmingham than in well-nourished persons.

Caries and Sugar Intake.—In all these studies, the most prominent common factor that might explain the lowered caries prevalence in areas of under-

nutrition and malnutrition is the marked decrease in refined sugar intake. The lowered prevalence of caries that follows a decrease in refined sugar intake seems to occur whether or not the other nutritional elements, including starches, are increased or decreased. The fact that refined sugar intake was always low in Italy and has been markedly decreased during the war, must, therefore, be given careful consideration and may well account for the low caries prevalence in spite of lowered nutritional levels and in spite of a very high starch intake. The per capita consumption of refined sugar per year in the prewar years of 1930-1934 was 18 lb. in Italy, as compared to 103 lb. in the United States (Intern. Inst. Agriculture, '36, cited from McCollum, Orent and Day, 1939, p. 616).

It is well established (Jay, 1940, 1944) that a reduction in carbohydrate intake will lower the incidence of caries (and possibly even arrest its progress). Although the Italian diet is predominantly carbohydrate in character, pasta (spaghetti, macaroni, etc.) and bread forming the major portion of their intake, the refined sugar intake is very low. Our findings thus seem to confirm the contention of Jay (1940), Schweigert and associates (1946) and others that people may eat freely of starchy foods and yet remain relatively free from caries provided *the intake of refined sugar is low.*

Unfortunately, *Lactobacillus acidophilus* counts of the saliva could not be made because of the lack of supplies.

Caries and Vitamin B Deficiency.—Another important factor that should be considered is that the children of Naples exhibited frank clinical signs of vitamin B deficiency. There are a number of reports which stress the relation between a low caries experience and vitamin B deficiency states. Dreizen and associates (1946) point out that both nicotinic acid and thiamine are necessary for the complete degradation of carbohydrates to acid end products. Their absence might serve to inhibit acid production in the mouth and therefore also inhibit caries. Mann and associates (1947) found a lowered caries prevalence in malnourished patients, many of whom showed prominent clinical signs of nicotinic acid and thiamine deficiencies.

The majority of the persons examined in Italy showed clinical signs of vitamin B deficiency. The reason for a very high incidence of clinical signs indicating vitamin B deficiency might be explained in part by the high carbohydrate diet. The latter diet requires more than average amounts of vitamin B complex for its metabolism. A slight deficiency in vitamin B intake would thus be aggravated by the high carbohydrate intake and result in more prominent clinical signs associated with vitamin B complex deficiency than would otherwise be the case.

Genetic Factors.—The importance of genetic factors in caries experience has been pointed out by Hunt and associates (1944) and Klein (1946). However, Day and Sedwick (1935) examined the teeth of 500 children 13 years of age of Italian descent living in Rochester, N. Y., whose diet, presumably, was now Americanized and high in refined sugar, and found no great difference between the incidence of caries in these children and the incidence in

American children. This latter study might lead to the conclusion that genetic factors are less important in the caries problem than is the character of the diet.

Fluorides.—The influence of fluorine as a factor in the low DMF experience can be eliminated here, since systemic mottled enamel was not seen and the water supply of Naples contained no significant amount of fluorine (0.2 parts per million).

Caries Susceptibility of Different Classes of Teeth.—Table III shows the distribution of caries among the incisors, bicuspids, and molars.

Anatomical Considerations.—Anatomical factors which are conducive to different degrees of stagnation or self-cleansing can explain some of the differences in susceptibility. In any given tooth, therefore, the pits and fissures are more susceptible to decay than are the smooth surfaces. Those smooth surfaces which may accumulate debris (contact areas, cervical areas) are more susceptible than self-cleansing areas (cuspal areas, occlusal two-thirds of buccal and lingual areas). These anatomic factors also account for the greater predilection of the posterior teeth (which have pits and fissures) to decay, than of the incisors, which are free of occlusal pits and fissures (Klein and Palmer, 1941).

Caries and Saliva.—However, when one compares the susceptibility of teeth with the *same* general anatomic characteristics, in the upper and in the lower jaws, a distinct difference in susceptibility is noted in the different arches. The lower molars are more susceptible to decay than are the upper molars, while the upper incisors are more susceptible than the lower incisors. The differences in caries susceptibility are considerable and significant and cannot be accounted for on an anatomic basis. One possible correlation that suggests itself is the fact that the salivary gland openings are located near the lower anterior teeth and near the upper posterior teeth. Both of these areas are significantly less susceptible to decay than the corresponding areas in the opposite jaw which are less apt to be bathed by saliva. Whether this is due to the detergent action of the saliva or to some bacteriostatic factor in the saliva remains to be determined.

The rare occurrence of caries on the palatal and lingual surfaces of the teeth may similarly be explained in part by their ready contact with saliva, aided by the mechanical action of the tongue. The labial and buccal surfaces, in contrast, are much more liable to cervical decay than the palatal and lingual surfaces since the saliva is displaced from the vestibule by the action of the lips and cheeks.

SUMMARY AND CONCLUSIONS

One hundred and sixty-two children, ages 10 to 18 years, living in Naples, were examined for dental defects in 1945-1946. The prevalence of caries experience was 1.67 DMF permanent teeth and 2.45 DMF permanent tooth surfaces per child. This is very low in comparison with that reported for similar age groups in the United States. Of the children, 35 per cent were caries free. Of the 65 per cent that suffered from dental decay, 83.8 per cent showed only the initial stages of caries which progressed slowly; 69 per cent of the first permanent molars were caries free

The prevalence of caries in children of similar ages in the United States is more than twice that observed in Neapolitan children. Since the latter were, for the most part, malnourished, the relation between good nutrition and a protective influence against dental caries is not borne out in this study. The low refined sugar intake in Italy and the high refined sugar consumption in the United States may, in part, explain the difference in the prevalence of caries. The rôle of vitamin B deficiency in depressing the incidence of caries should also be considered.

REFERENCES

Bodecker, C. F.: The Modified Dental Caries Index, J. A. D. A. 26: 1453, 1939.

Boyd, J. D., and Cheyne, V. D.: To What Extent Does Fluorine Ingestion Lessen Tooth Decay? Am. J. Dis. Child. 29: 286, 1946.

Cady, F. C.: Dutch Children in Coventry, Oral Hygiene 36: 246, 1946.

Collett, A.: Nordisk Medicin, June 7, 1946, Cited from Dental Benefits of War, Lancet 251: 129, 1946.

Day, C. D. M.: Nutritional Deficiencies and Dental Caries in Northern India, Brit. Dent. J. 76: 115, 143, 1944.

Day, C. D. M., and Sedwick, H. J.: Studies on the Incidence of Dental Caries, D. Cosmos 77: 442, 1935.

Dreizen, S., Mann, A. W., Cline, J. K., and Spies, T. D.: The Buffer Capacity of Saliva as a Measure of Dental Caries Activity, J. Dent. Res. 25: 213, 1946.

Flumerfelt, R.: Unpublished.

Friel, Sheldon: The Effect of the War Diet on the Teeth and Jaws of the Children of Vienna, Austria, Int. J. Orthod., O. S., and Radiogr. 8: 539, 1922.

Hunt, H. R., Hoppert, C. A., and Erwin, W. G.: Inheritance of Susceptibility to Caries in Albino Rats (Mus Norvegicus), J. Dent. Res. 23: 385, 1944.

Jay, Philip: The Rôle of Sugar in the Etiology of Dental Caries, J. A. D. A. 27: 393, 1940.

Jay, Philip: Nutrition and Dental Caries, N. J. Dent. Soc. J. 15: 20, 1944.

Klein, H.: The Family and Dental Disease: IV. Dental Disease (DMF) Experience in Parents and Offspring, J. A. D. A. 33: 735, 1946.

Klein, H., and Palmer, C. E.: The Dental Problem of Elementary School Children, Milbank Mem. Fund. Quart. 16: 267, 1938.

Klein, H., and Palmer, C. E.: Studies on Dental Caries: XII. Comparison of the Caries Susceptibility of the Various Morphological Types of Permanent Teeth, J. Dent. R. 20: 203, 1941a.

Klein, H., and Palmer, C. E.: On the Epidemiology of Dental Caries: Dental Caries, Univ. of Penn. Press, Philadelphia, pp. 1-25, 1941b.

Knutson, J. W., Klein, H., and Palmer, C. E.: Studies on Dental Caries: VIII. Relative Incidence of Caries in Different Permanent Teeth, J. A. D. A. 25: 1923, 1938.

Kyhos, E.: Unpublished.

Mann, A. W., Dreizen, S., Spies, T. D., and Hunt, F. M.: A Comparison of Dental Caries Activity in Malnourished and Well-Nourished Patients, J. A. D. A. 34: 244, 1947.

Massler, Maury: Teen-Age Caries, J. Dent. Child. 12: 57, 1945.

McCollum, E. V., Orent-Keiles, E., and Day, H. G.: The Newer Knowledge of Nutrition (5th ed.), New York, 1939, The Macmillan Co., p. 616.

Morgan, H. J., Wright, I. S., and von Ravenswaay, A.: Health of Repatriated Prisoners of War from the Far East, J. A. M. A. 130: 995, 1946.

Oliver, D. H.: Some Evidence of Wartime Reduction of Caries Incidence in Children, Brit. Dent. J. 80: 115, 1946.

Schour, I., and Massler, M.: Dental Caries Experience in Postwar Italy: I. Prevalence in Different Age Groups, J. A. D. A. 35: 1, 1947.

Schweigert, B. S., Potts, E., Shaw, J. H., Zepplin, M., and Phillips, P. H.: Dental Caries in the Cotton Rat: VIII. Further Studies on the Dietary Effects of Carbohydrate, Protein and Fat on the Incidence and Extent of Carious Lesions, J. Nutrition 32: 405, 1946.

RABIES

A Case Report with Notes on the Isolation of the Virus from Saliva

Carl E. Duffy, Ph.D., Paul V. Woolley, Jr., M.D., and
Wilfred S. Nolting, M.D.

With the Technical Assistance of

Norma H. Feeley
Detroit, Mich.

ACCURATE clinical accounts of rabies in childhood have been recorded so frequently in medical literature that it would appear nothing new could be gained through further case reports. However, a recent incident illustrated how confusing the diagnosis can be when a clear-cut history of exposure is not obtained, and also provided an opportunity for some rather unique and practical laboratory observations.

The patient, a 13-month-old boy, was brought to the hospital because of fever, refusal of food, irritability, restlessness, and disorientation, all of twenty-four hours' duration. He had been well previously and had developed in a manner befitting his chronologic age. The only unusual event was an injury sustained some five weeks earlier when he supposedly had fallen upon a toy while playing in his pen. This had resulted in an irregular laceration on the upper lip which had necessitated the placing of several sutures by the attending physician. At the time of admission the wound had healed, leaving a reddened, nonindurated scar.

Examination showed the child to be overactive, apprehensive to the point of clinging constantly to the examiner, and completely divorced from his surroundings. His hands moved constantly in a purposeless manner and he would neither sit nor stand. There was no stiffness of the back or neck and the reflexes were not noted to be abnormal. His pupils reacted to light, although one was seen to be slightly larger than the other. The fundi were easily visualized and appeared intact. There was no impairment of hearing, swallowing, or vocalization. The rectal temperature was 103° F., blood pressure 120/80, pulse 100 per minute, and nothing out of the ordinary was found during the remainder of the examination.

Laboratory data at the time of admission included a normal urine, hemoglobin of 12 Gm. per 100 c.c. of blood, 7,200 white cells per cubic millimeter with 40 per cent polymorphonuclear leucocytes, 58 per cent lymphocytes, and 2 per cent monocytes. The Mazzini test was negative, as was also the reaction to a 1:100 dilution of tuberculin. Cerebrospinal fluid, obtained under pressure

From the Virus Laboratories of The Children's Fund of Michigan, The Children's Hospital of Michigan, and the Departments of Bacteriology and Pediatrics, Wayne University College of Medicine.

of 200 mm. of water, contained a normal amount of sugar, no demonstrable globulin, and 13 mononuclear cells per cubic millimeter. No growth was obtained in cultures of blood or cerebrospinal fluid.

The child's behavior during the first hospital day was described as fretful and hyperactive. He did not recognize his parents but seemed in no pain or distress. He was able to take liquids and his temperature remained around 103° F. Treatment was limited to sedation with paraldehyde and the administration of fluids parenterally. An encephalitis of unknown cause was thought the best explanation for his condition, and the parents were recalled for further questioning in the hope of eliciting information which would aid in establishing an etiologic factor. Trauma, exposure to tuberculosis or mumps, contact with lead or other poisons, environmental prevalence of rodents or birds, and the existence of infectious disease in the other members of the family were touched upon without enlightenment. Questioning was then directed to the incident five weeks earlier, and the story, as reconstructed, was that a recently acquired pup, 7 months of age, had acted peculiarly on the day in question. It was thought that she was in heat and when she disappeared in the evening it was assumed that she had been retained by her finder. Concentrated efforts to locate the animal, then, as well as at the time the child was hospitalized, were to no avail, despite cooperation by newspapers, newscasts, police, humane organizations, and health agencies. Although it appeared clear that the dog had not been in free contact with the patient, it seemed possible that she could have inflicted the wound, had the infant presented his face at the play-pen bars. With this possibility in mind, saliva was collected and utilized as described later in this presentation. Conversation with the breeder from whom the dog was obtained disclosed that the animal had not received antirabic prophylaxis but had been confined closely and that there had been no symptoms among kennel mates.

Periods of hyperexcitability alternating with periods of sleep characterized the third day of illness and the temperature remained at 103° F. Muscular twitching and labored respiration accompanied the hyperactive episodes, and at times the child cried out. Treatment was again limited to fluids, including 60 c.c. of plasma parenterally, and sedation. On the fourth day of symptoms the child was somewhat quieter but his pulse was extremely rapid, the temperature continued at 103° F. and twitching of the muscles was noted on occasion. He lay with his eyes open even when sleeping but made no effort to fix upon his surroundings. He was able to swallow and took 8 oz. of water during the course of the morning. A lumbar puncture was done and the fluid obtained was identical in constitution with that reported earlier. A urinalysis was also uninformative. The fifth day was not greatly different from the preceeding, and, if anything, the patient appeared more quiet and seemed to pass into normal sleep between periods of increased activity. He still was capable of taking sips of water and treatment again consisted of fluids, including plasma parenterally and sedation. From the sixth to the ninth day of illness there was no dramatic departure from the earlier course. Periods of muscular excitability alternated with moments when he slept. Respiratory difficulty

was noted rarely and only during the periods of spasm while no true dysphagia was encountered. Occasionally the pulse appeared extremely rapid and for brief periods abdominal distension was troublesome. Despite sponging and antipyretics the temperature fluctuated only rarely from 103° F. As the child remained essentially unchanged day after day, the diagnosis of rabies was entertained less seriously, especially when a re-examination of the cerebrospinal fluid on the eighth day of the disease showed 110 cells, of which 90 per cent were mononuclear, and 93 mg. of protein per 100 c.c. The sugar and chloride determinations on the same specimen were within normal range. Encephalitis due to agents other than rabies, a bizarre form of tuberculous meningitis, or even a diffuse medulloblastoma were again considered. However, on the following day, the tenth of symptoms and the ninth of hospitalization, he was considerably weaker and peripheral vascular collapse seemed imminent, although he appeared much more alert and would focus on objects for short periods of time. During the night he experienced the first true difficulty with swallowing and early in the morning expired apparently while sleeping quietly. Permission for an autopsy was denied, so that our impression could not be extended beyond encephalitis of unknown etiology.

LABORATORY STUDIES

On the fourth day after the development of symptoms and seven days before the infant expired, samples of spinal fluid, blood, and saliva were obtained.

The spinal fluid was immediately injected into ten 3- to 4-week-old Swiss mice. All received 0.03 c.c. intracerebrally and seven of the ten received, in addition 0.4 c.c. intraperitoneally. The mice were observed daily for sixty-six days and remained well throughout the observation period.

The blood was allowed to clot and was then stored at 4° C. to 6° C. for approximately forty-eight hours. It was then centrifuged and the serum removed. The serum was transferred to a 10 c.c. screw-cap bottle and stored in a dry-ice cabinet. After twenty-nine days' storage in the dry-ice cabinet, the serum was removed and thawed in a water-bath at 37° C. The serum was then inoculated intracerebrally into Swiss mice. Each of eight mice were injected intracerebrally with 0.03 c.c. of the serum. These eight mice remained well throughout the observation period of sixty days.

The saliva was obtained while the child was under paraldehyde sedation. The head was turned to one side and the saliva was aspirated with a medicine dropper as it collected on the inner surface of the cheek and under the tongue. Approximately five minutes were spent in collecting about 0.8 c.c. of saliva. The saliva was immediately taken to the laboratory and injected into 3- to 4-week-old Swiss mice. Each of eight mice were injected intracerebrally with 0.03 c.c. of untreated saliva. To 0.5 c.c. of the saliva, 1,000 units of penicillin were added. After mixing the saliva and penicillin 0.03 c.c. of the mixture was injected intracerebrally into each of seven mice. Two additional mice were injected intraperitoneally with 0.1 c.c. of the penicillin-treated saliva. The results appear in Table I. All of the mice which were injected with the untreated saliva died within twenty-four hours. Gram stains of impressions of the

TABLE I. FATE OF MICE INOCULATED WITH SALIVA

MATERIAL INOCULATED	ROUTE OF INOCULATION	NUMBER INOCULATED	RESULTS*
Untreated Saliva	Intracerebrally	8	1, 1, 1, 1, 1, 1, 1, 1
Saliva plus penicillin	Intracerebrally	7	3, 4, 5, 7, 15†, 16†, 16†
Saliva plus penicillin	Intraperitoneally	2	S, S.

*Under results a numeral indicates day of death. The letter "S" indicates survival.
†These mice showed signs of encephalitis and were sacrificed for passage to other mice.

brains of these mice revealed a mixture of Gram-negative and Gram-positive bacteria. Several of the brains were stored at 4° C. to 6° C. in 50 per cent glycerine-saline but were not investigated further because of subsequent findings in the mice which were injected intracerebrally with the penicillin-treated saliva.

All of the seven mice which had been inoculated intracerebrally with the treated saliva appeared sick the following day. Their hair was ruffled and they were less active than normal mice of the same age. On the second day, four of the mice had recovered and again appeared healthy. Of the remaining three, one died on the third day, one on the fourth day and one on the fifth day of bacterial infection. One of the four mice which had been injected intracerebrally with the penicillin-treated saliva, and which appeared sick twenty-four hours later but seemed to have recovered by the second day, was found dead on the seventh day, after it had been inoculated. The brain of this animal was not recovered since it had been eaten by the remaining mice. Of the three remaining mice which had been inoculated intracerebrally with the penicillin-treated material, one developed symptoms suggesting rabies encephalitis on the fifteenth day and the other two showed similar symptoms on the sixteenth day. The mouse which had developed symptoms on the fifteenth day was sacrificed. The brain was removed and ground in a mortar with 4 c.c. of saline. The suspension was allowed to stand at room temperature until the large particles settled out and then the supernatant liquid was inoculated intracerebrally into eight mice. Of these latter eight mice, two were found dead on the eighth day and the remainder showed symptoms of encephalitis. A touch preparation of the brain of one of the animals which had developed encephalitis was stained with Seller's stain and Negri bodies were observed.

The two mice which developed symptoms of encephalitis sixteen days after they had been injected intracerebrally with penicillin-treated saliva were sacrificed on the same day they developed symptoms. The brains were removed and ground together in a mortar with 8 c.c. of saline. The supernatant liquid from this suspension was then inoculated intracerebrally into seven mice. One of the seven mice was found dead eight days later and the remaining six showed symptoms of encephalitis. Negri bodies were demonstrated in a touch preparation of the brain of one of these mice. The brain of an additional mouse was fixed in 10 per cent formalin. Sections from the hippocampus of this brain, when stained with hemotoxylin-eosin revealed intracytoplasmic inclusion bodies in the nerve cells.

The two mice which were injected intraperitoneally with the penicillin-treated saliva remained well throughout the sixty-six day observation period.

The demonstration of Negri bodies in the brain of man and other animals is accepted as sufficient evidence to make a diagnosis of rabies. However, in the present study it seemed that the agent isolated should be further identified particularly since it was recovered from an extraneural source. Therefore, a neutralization test was performed to determine whether hyperimmune rabies antiserum* would neutralize the virus. Simultaneously, the serum of the infant, obtained four days after the onset of symptoms, was tested against the agent isolated from the saliva to determine whether it contained neutralizing antibodies. A 20 per cent suspension of mouse brain infected with the agent isolated from the saliva was prepared by grinding the brain in a mortar with sand and a mixture composed of 10 per cent rabbit serum and saline. Further tenfold dilutions of the 20 per cent brain suspension were prepared using 10 per cent rabbit serum-saline as a diluent. The dilutions of virus to be tested were added, in 0.2 c.c. amounts, to Kahn tubes containing 0.2 c.c. of the serum to be tested. The tubes containing serum were kept in an ice water bath while the virus was being added. Following the addition of the virus, the serum-virus mixtures were incubated in a water bath at 37° C. for two hours. The tubes containing the serum-virus mixtures were then placed in an ice water bath and the mixtures were then immediately injected intracerebrally into mice. Normal rabbit serum was used as a control. The results appear in Table II. It will be observed that the agent isolated was neutralized by the rabies hyperimmune serum, thus confirming the evidence obtained by histologic studies. The serum of the infant contained little or no antibody since the LD/50 titer[1] of the agent mixed with the infant's serum was about the same as that obtained when the virus was mixed with normal rabbit serum.

TABLE II. SEROLOGICAL IDENTIFICATION OF THE VIRUS

SERUM TESTED	DILUTIONS OF VIRUS							LD/50 TITER NEGATIVE LOG. OF DILUTION	NEUTRALIZATION INDEX*
	10^{-1}	10^{-2}	10^{-3}	10^{-4}	10^{-5}	10^{-6}	10^{-7}		
Normal rabbit serum (control)	—	4/4†	3/4	2/5	0/5	0/5	0/5	3.7	—
Patient's serum	5/5	5/5	3/4	0/4	0/5	—	—	3.3	3
Hyperimmune rabies antiserum	1/5	0/4	0/5	0/5	0/4	—	—	0.6‡	>1260

*Neutralization index = antilog $\frac{\text{LD/50 titer of virus mixed with normal rabbit serum}}{\text{LD/50 titer of virus mixed with serum being tested}}$

†Denominator denotes number of mice tested and the numerator denotes the number of deaths.

‡No LD/50 end-point was obtained. This figure was obtained by assuming that if a tenfold lower dilution of the virus were tested all the animals would have died.

DISCUSSION

The diagnosis of rabies is so intimately connected with a history of animal bite that the present case proved a revelation to us since, in the absence of a

*The hyperimmune rabies antiserum was obtained through the courtesy of Dr. F. D. Stimpert of Parke, Davis and Company.

definite exposure, we found so little upon which to base a conclusive argument. The clinical observations, physical findings, and laboratory data revealed nothing to be construed as specific to the disease. Certainly, periods of hyperexcitability and hyperactivity alternating with moments of sleep or coma are parts of a variety of syndromes, including most of the virus encephalitides and tuberculous meningitis, while a prolonged febrile course without dramatic laboratory findings likewise fits a number of diseases of the central nervous system. We were especially disappointed in the lack of similarity to tetanus or botulism, conditions with which rabies is said to be frequently confused. The cerebrospinal fluid change, a gradually developing pleocytosis with a predominance of lymphocytes, is again hardly diagnostic and definitely not in accord with the texts where findings vary from no change to a cellular increase attributable to the polymorphonuclear fraction.[2, 3] Finally, rabies is usually described as a disease characterized by difficulty in swallowing (hydrophobia) with death intervening in less than five days from progressive paralysis. In this instance, however, the patient survived eleven days with little evidence of dysphagia and a complete lack of progressive deterioration. In fact, had it not been for contributions from virus studies, this record would have joined many others in the scrapbasket of, "encephalitis of unknown etiology."

While rabies virus has been isolated from the saliva of man,[4-7] this is, to the best of our knowledge, the first instance in which the dianosis of rabies in man has been established by recovering the virus from the saliva. In the case here reported there was no definite history of a bite and in addition there was no opportunity to study the infant's brain either for lesions or virus since an autopsy was not permitted. Therefore a definite diagnosis would not have been made if the virus had not been recovered from the saliva.

The frequency with which rabies virus is present in the saliva of human cases of rabies is not known. Palawandow and Serrebrennja[4-6] isolated the virus from the saliva of four of five patients studied and Sulkin and Harford[7] reported positive results in one of two patients. Sabin and Ruchman, in studying the distribution of the virus in an unvaccinated case, did not find the virus in the saliva.[8] Whether the reported failures to isolate the virus from the saliva have been due to inadequate methods or to the absence of the virus from the saliva of some cases cannot be stated. However, the positive findings reported here, as well as those of Palawandow and Serrebrennja and of Sulkin and Harford, suggest that in human cases the virus may frequently be present in the saliva. Perhaps with improved methods, more positive results will be obtained.

The studies of Pawan[9] would suggest that the etiologic agent of paralytic (Trinidad) rabies is frequently present in the saliva of human patients, since he was able to recover the virus from the saliva of all of the six patients studied. Swabs which had been moistened with saliva were rubbed into the scarified skin of rabbits. The animals became paralyzed and histologic studies revealed Negri bodies in the brains of the animals.

It would appear at present that if rabies virus is to be isolated from the saliva by intracerebral inoculation into mice, the saliva should be treated first

in order to minimize the chances of causing a bacterial infection in the mice. Sulkin and Harford[7] isolated rabies virus from saliva which had been treated with ether and in the present study virus was isolated from saliva to which penicillin was added. Perhaps in future attempts to isolate rabies virus from the saliva of man a portion of the saliva should be treated with ether and another with penicillin or other bacteriostatic agents before inoculation into mice.

The finding of the virus of rabies in the saliva of man indicates that the disease may be transmitted through the bite of a rabid individual. Koch[10] has referred to two cases in which rabies was transmitted from one person to another. In one instance the disease may have been contracted during coitus and in another the disease developed following the bite of a rabid individual. The diagnosis in these two cases, however, is not unequivocal, particularly since they occurred prior to Negri's[11] demonstration of the association of intracytoplasmic inclusion bodies in the nerve cells with rabies. Kraus, Gerlach, and Schweinburg[12] have pointed out the discordance in the results and opinions concerning infectivity of saliva and added that no case of rabies has been known to be produced by the bite of a human being. However, as Sulkin and Harford[7] have pointed out, those who are in close contact with rabid individuals should take due precautions to prevent the saliva from entering wounds and abrasions.

One other point should be discussed at this time. Sulkin and Harford[7] obtained the saliva, from which they isolated rabies virus, from the patient during a convulsive seizure at a time when there was a copious flow of saliva. On the other hand, they failed to recover the virus from another case in which saliva was obtained by swabbing the mouth. From these findings Sulkin and Harford suggested that only a copious flow of saliva may contain sufficinet virus to be detected. That this is not necessarily true is apparent from the case reported here. The saliva was obtained at a time when the infant was under paraldehyde sedation and when there were no muscular twitchings or trismus. The saliva was not abundant since considerable time was spent in obtaining a sufficient quantity for animal inoculation.

SUMMARY

1. The history of an infant with a clinically undiagnosed disease of the central nervous system is recorded. While the possibility of a dog bite was recognized, nothing specific of rabies was descernible.

2. The diagnosis of rabies was established by isolating rabies virus from the saliva.

3. The untreated saliva when injected intracerebrally into mice, killed the animals within twenty-four hours.

4. The same saliva when mixed with penicillin and inoculated intracerebrally, permitted three of the seven mice inoculated to survive long enough so that the virus could be recovered.

5. The agent isolated from the saliva was shown to be rabies virus by demonstrating Negri bodies in the brains of mice and by neutralizing tests.

6. The virus was not isolated from the cerebrospinal fluid or blood.

REFERENCES

1. Reed, L. J., and Muench, H.: Am. J. Hyg. **27**: 493, 1938.
2. Levinson, A.: Cerebrospinal Fluid in Health and Disease, ed. 2, St. Louis, 1929, The C. V. Mosby Company, p. 317.
3. Van Rooyen, C. E., and Rhodes, A. J.: Virus Diseases of Man, London, 1940, The Oxford University Press, p. 640.
4. Palawandow, H., and Serebrennaja, A. I.: Ztschr. f. Immunitätsforsch. u. exper. Therap. **66**: 519, 1930.
5. Palawandow, H., and Serebrennaja, A. I.: Ztschr. f. Immunitätsforsch. u. exper. Therap. **68**: 236, 1930.
6. Palawandow, H., and Serebrennaja, A. I.: Ztschr. f. Immunitätsforsch. u. exper. Therap. **71**: 350, 1931.
7. Sulkin, E. S., and Harford, C. G.: Ann. Int. Med. **19**: 256, 1943.
8. Sabin, A. B., and Ruchman, I.: Proc. Soc. Exper. Biol. and Med. **44**: 572, 1940.
9. Pawan, J. L.: Ann. Trop. Med. and Parasitol. **31**: 267, 1937.
10. Koch, J.: Handbuch der pathogenen Mikro-Organismen, 1930, vol. 8, p. 553.
11. Negri, A.: Ztschr. f. Hyg. **43**: 507, 1903.
12. Kraus, R., Gerlach, F., and Schweinburg, S.: Lyssa bei Mensch und Tier, Vienna, 1926, pp. 80, 128-131. (Quoted from Sabin and Ruchman).

THE PRIMARY ETIOLOGY OF THE SPECIFIC LANGUAGE DISABILITIES

RICHARD S. EUSTIS, M.D.
BOSTON, MASS.

MANY a healthy and intelligent person has been forced to modify his plans for the future because of defective speech or because he found it impossible to absorb knowledge from books fast enough to keep up with his school or college program. This problem of comparative disability in the use of language is a common one and often serious. It has been studied exhaustively by educators, psychologists, psychiatrists, neurologists, and pediatricians. The resulting literature is voluminous but conflicting. It proposes many theories of causation, none of which has been widely accepted.

The specific* language disabilities consist of specific reading disability, speech defects, such as lisping and stuttering, and motor speech delay.† Most investigators report that two or more are often found in the same individual. Most also find that ambidexterity or left-handedness, and unusual bodily clumsiness, are commonly associated conditions. Others find no relationship. Some report a definite familial incidence, which is vehemently denied by others. Almost the only point of complete agreement is that the picture is commoner in boys than in girls by the ratio of at least 3:1.

The pediatrician, seeking understanding of the problem for himself as well as practical aid for his patients, is left thoroughly bewildered.

The familial incidence of the syndrome has been so strongly denied that it is necessary to go into further detail and give some of the arguments pro and con.

Witty and Kopel,[1] and Blau,[2] have collected and summarized the many statistical reports which seem to refute the influence of heredity on the picture. These reports are based very largely, however, on results obtained by questionnaires. Any physician knows how difficult it is to obtain a trustworthy history of the incidence of common diseases in the family. The staff of the Language Clinic has found it even more difficult, because only the extreme instances of language disability and ambidexterity have been noticed and remembered. It is not uncommon for a parent with obviously defective speech to deny the existence of any such in the family. Therefore, the negative evidence of these reports may be partly, at least, discounted.

On the other hand, the evidence in favor of the familial nature of the syndrome is impressive. Scattered through the literature are very many case reports mentioning the existence of similar disabilities in other members of the

From the Language Clinic, Massachusetts General Hospital.

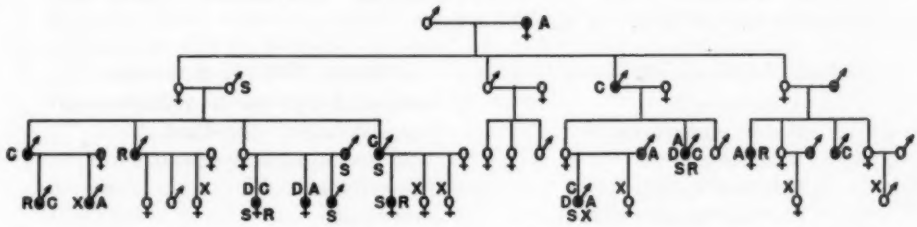
*Excluded are language disabilities due to injuries, disease, or physical or mental abnormalities.

†So termed to distinguish it from late development of speech due to physical or mental abnormalities.

families. Statistical proof of the familial incidence of stuttering and left-handedness is supplied by Berry,[3] Nelson,[4] and West.[5] Family trees showing an incidence of disability of approximately 40 per cent have been published by Orton[6] and by Cobb.[7] The positive evidence appears too well authenticated to be discarded.

Another family tree is offered as further proof. Every member through four generations has been personally known by the writer. Some of the third generation and most of the fourth have been carefully studied as well. (See Fig 1.)

FAMILY TREE, SHOWING INCIDENCE OF
LANGUAGE DISABILITIES AND ASSOCIATED CONDITIONS



Infants under 2 years omitted
X — under 6 years
● — Disability
◐ — Disability in family
A — Left-handed or ambidextrous
C — Clumsy
D — Motor Speech Delay
R — Specific Reading Disability
S — Speech Defect

Fig. 1.

Of thirty-three descendants over 2 years old, fourteen (42 per cent) show one or more of the disabilities. Of twenty-five descendants over 6 years old,* twelve (48 per cent) show one or more of the disabilities. Most of these disabilities are comparatively mild.

Obviously, neither ambidexterity nor left-handedness is any great drawback to a successful life. Unusual bodily clumsiness merely leads to a lack of prowess on the athletic field. Motor speech delay by itself is of no great import, although it frequently precedes defective speech. None of the latter in this series have been severe.

Specific reading disability, on the other hand, has been a great handicap to the three boys afflicted by it. In the three girls it has been much milder and has responded much more quickly to remedial training.

This brief review leaves us puzzling over the origin and the nature of a familial syndrome found in otherwise normal persons, chiefly males. It comprises at least five apparently unrelated symptoms: bodily clumsiness, left-handedness and ambidexterity, late development of speech, lisping and stuttering, and specific reading disability. These occur singly or in any combination

*Old enough to show whether or not they are going to have trouble with reading.

of two or more. Some individuals show all five. Frequently, only one has been noticed, and one or more of the others are discovered later by questioning, observation, and testing.

One way of attacking the problem is to consider it as a whole, as a syndrome of frequently associated symptoms, instead of treating each aspect as a separate entity. When this is done, it becomes obvious that they all, because of their frequent association in the individual and in his family tree, must develop from some common and underlying cause. This much has been suggested by West[5] and a possible underlying cause for infantilisms, stuttering, and motor speech delay has been offered by Karlin and Kennedy[8] and by Berry.[3]

An apparently significant point is that all these symptoms are found normally in infants and young children. Only when they persist into later childhood and adult life do they attract attention. This becomes obvious when the symptoms are listed in parallel columns.

Normal Infant and Young Child	*Patient With the Syndrome*
Ambilateral*	Left-handed or partly ambidextrous†
Bodily clumsiness	Unusual bodily clumsiness
No speech	Late development of speech
Infantile speech	Infantilisms
Stutters under excitement	Stuttering
Unable to read	Specific reading disability

The various aspects of the syndrome are thus seen to be the result of a rather specialized delay in development. The problem is to find a probable cause for this delay.

Several authors give a clue as to what it may be. Karlin and Kennedy[8] mention a slow rate of neural myelination as a possible cause of delayed development of speech and of stuttering. Berry[3] refers to it as a possible cause of both motor speech delay, and of infantilisms and defective speech. They offer, however, no proof that myelination actually is retarded in these conditions. The most that can be said is that it is widely believed that neuromuscular maturation and myelination are closely associated in the growing infant and young child. Langworthy[9] presents some proof that such is the case.

Common observation tells us that the normally intelligent children of some families tend to master the simple motor skills of early childhood either more quickly or more slowly than the average. There must be, therefore, a familial tempo of neuromuscular maturation underlying the well-recognized individual tempo. If it can be shown that an unusually slow tempo may affect boys more than girls, and may tend to produce the different aspects of the syndrome, we shall have a single, simple, and intelligible hypothesis in place of the present confusion.

Before preceeding further, it is necessary as a background to outline briefly the normal development of handedness, bodily skill, and speech in the average child.

*Equally clumsy with both hands.
†Most sinistrals have more than usual skill in the nonpreferred hand.

The young infant is not ambidextrous but rather ambilateral, equally clumsy with both hands.[2] By the end of the first year, neuromuscular maturation has progressed sufficiently for him to have developed some skill in both. The first signs of unilateral-handedness and of speech appear about then or during the second year. The choice of the preferred hand, weak at first, gradually strengthens through the years. Laterality statistics on preschool, grammar school, and high-school children and on adults show a constantly diminishing amount of left-handed skill,[2] facts which suggest that the inheritance factor in handedness, even if originally present, is not very strong, except, perhaps, in the few (1 to 5 per cent) individuals who persist in their sinistrality.

Why the right hand is usually chosen is not known with any certainty. Most favor inheritance as the reason, some the precept and example of life in a right-handed world.* Even the supporters of the inheritance theory agree that the latter influence swings many whom they consider were originally left-handed over to the right. It seems quite clear that the confirmation, if not the origin, of unilateral handedness is largely a developmental process, habitual use constantly strengthening the original choice.

From textbooks and articles on histology[9-11] and physiology[12] we learn the following pertinent facts about the myelination of the nervous system: Some muscular activity is possible before myelination begins, but the responses are slow, weak, and diffuse. The rate of myelination is greatly accelerated at the time of birth, suggesting that functional use stimulates the process. The myelination of the different tracts follows a definite sequence. Each tract has its own rate of myelination. It is not completed in the corticospinal tracts until the second year, in the spinal nerves until the third year, and in the association fibers until still later. In the cord it is not completed until between the fifteenth and twentieth years. It develops simultaneously in the fibers of different, although functionally related, tracts. Since Flechsig, it has been generally believed, although not definitely proved, that full functional activity of a medullated nerve depends upon the completion of its myelination.

From textbooks and articles[9,13,14] on child development we learn the following about neuromuscular maturation: In normal infants and young children the various skills appear in fairly definite sequence. The rate of development varies from child to child, each possessing his individual tempo. In general, girls are one or more months ahead of boys. It is widely believed, although not absolutely proved, that the full attainment of any particular skill depends first upon the myelination of the motor and association tracts concerned, and second upon practice. Langworthy[9] strengthens this belief by a long list of sensory and motor functions in the newborn and young infant, correlating their presence at birth or their appearance in the early months of life with the myelination of the nerve tracts concerned.

Obviously, myelination and neuromuscular maturation are closely related and probably mutually dependant on each other. If this is so, the observable development of neuromuscular maturation may be regarded as an indicator of the unseen development of myelination.

*No one knows why the world is predominantly right-handed.

This information from the laboratory and from the nursery leads us directly to several assumptions, unproved but logical: (1) myelination is completed earlier in girls than in boys; (2) because of the common observation that the children of certain families tend to develop either faster or slower than the average, there is a tendency to a familial rate of myelination; (3) each infant has his individual tempo of myelination associated with his individual tempo of neuromuscular maturation; (4) unusually early or unusually late neuromuscular maturation in normal children in normal environments implies equally early or late myelination; (5) when one particular skill appears out of the normal order, either earlier or later than usual, it implies a correspondingly early or late myelination of the particular motor and association tracts needed for that skill.

With these assumptions in mind as a working hypothesis, let us consider, one by one, the various aspects of the syndrome under consideration and the part that a delay in neuromuscular maturation may play in their development.

AMBIDEXTERITY

Slow maturation, by prolonging the period of infantile ambilaterality, gives both hands time to acquire some skill. Habitual use of both hands for several years in early childhood will result in the child's carrying into adult life an unusually large amount of skill in the nonpreferred hand, regardless of whether he finally becomes mainly right or mainly left-handed. Thus, delayed neuromuscular maturation will account for ambidexterity.

LEFT-HANDEDNESS

A prolonged period of ambilaterality, perhaps lasting until the child is 6 years old, instead of fading gradually soon after the first year, inevitably raises the question of whether or not he may be left-handed. This doubt, present in the minds of those about him, often results in the left hand being chosen for training. He will then be regarded by the world as a left-hander, although retaining considerable, often unnoticed, skill in the right hand. This is one, although probably not the only, explanation of left-handedness.

UNUSUAL BODILY CLUMSINESS

When good neuromuscular control is slow in developing, the period of childhood awkwardness is prolonged. Body and hands are manipulated poorly for a longer than usual time, and habitual use tends to fix and perpetuate the clumsiness, particularly in the simple skills which were learned in early childhood. This does not mean that the individual is incapable of acquiring considerable or even expert skill in later childhood. It does suggest that the period of training may be longer and more difficult than in those in whom neuromuscular maturation developed at the normal rate. The end result may be a comparatively clumsy individual who has attained through training and effort considerable skill in certain lines.*

*An extremely clumsy and awkward boy became a successful pilot of large planes during the war, although he is still clumsy and apt to drop and break things in civilian life.

SPECIFIC LANGUAGE DIFFICULTIES

These all may be regarded as more localized forms of general bodily clumsiness affecting specifically the neuromuscular control of speech and, in specific reading disability, the direction of eye gaze.

Motor Speech Delay.—It is obvious that speech is impossible until neuromuscular maturation has progressed to the point where there is good control over the muscles used in talking. Therefore, a slow rate of maturation will inevitably retard the development of speech. This point has already been made by Karlin and Kennedy[8] and by Berry[3] when they suggested that retarded myelination might be the cause of motor speech delay.

Infantilisms.—The speech of small children normally is full of defects to which we pay no attention. These defects are sound substitutions, such as *w* for *r*, and *th* for *s*, and sound omissions. They also not uncommonly reverse, as *overlaws* for *overalls*. When these defects persist into late childhood and adult life they are classed as infantilisms. Slow development of skill in speaking due to a slow tempo of maturation gives some of these defects a chance to become fixed by habitual use and hence will account for the frequency of infantilisms in the syndrome.

Stuttering.—Under sufficient stress almost anyone may stutter. These children do so under minor stress and are apt to begin their stuttering at one of three special periods of rapid development. Commonly it is soon after they begin to talk, less often when they begin to read, and occasionally it develops during adolescence when much more is expected of both speech and reading. It also may appear first after a fright, an accident, or an illness, any one of which may act as the stimulus which turns a potential into an actual stutterer.

Delayed neuromuscular maturation has equipped the potential stutterer with a speech mechanism which functions too slowly and clumsily to keep up with the rapidly increasing flow of ideas demanding utterance. Under strain it momentarily breaks down entirely, as in speech block, or becomes disorganized, as in the meaningless repetition of a single sound. The effort to force speech then produces an overflow of nervous energy which shows itself in the well-known bodily tensions, contortions and grimaces. After a few failures the emotional element enters the picture, and well-justified fear of stuttering tends to perpetuate the habit.

The poor athlete, the poor dancer is only slightly affected by his disability, but the stutterer is severely crippled in his relations with his fellows. It is easy to understand why the emotional element in stuttering bulks so large and is regarded by many as the fundamental cause.

Specific Reading Disability.—The essence of specific reading disability is an uncertainty in spatial orientation (Blau), a confusion between the right-left and the left-right directions, showing itself as a tendency to reverse at irregular intervals the direction of eye gaze. Many children do this when they first start to read, particularly if they are taught by the "look and say" method instead of phonetically, but most correct themselves within a few weeks or months. Evidently a certain amount of spatial confusion may be present normally in first grade children.

A prolonged period of ambilaterality in early childhood, during which the two hands are used more or less interchangeably, leaves the individual with a more severe and lasting confusion between right and left. The slower the neuromuscular maturation, the longer the period of confusion; the longer the period of confusion, the more likely is the individual to establish and fix as a habit the occasional and momentary reversal of the direction of eye gaze from left-right to right-left. These reversals lead either to failure in learning to read or to such slow and faulty reading that the child is unable to comprehend what he does decipher. When such children discover that they are being left behind by others no brighter than they, the emotional element, as in stuttering, enters and confuses the picture. Thus a slow rate of neuromuscular maturation, by prolonging the normal period of spatial confusion in hand and eye, seems to be the primary cause of specific reading disability.

PREPONDERANCE OF MALES

On the average, the neuromuscular maturation of boys is slower than that of girls. They are usually a month or more later in mastering the simple motor skills of childhood. By and large they are apt to remain less graceful than girls through adolescence or even for life. Obviously, the same degree of retardation of neuromuscular maturation in a boy and a girl will affect the boy more severely and hence will account for the preponderance of males in the syndrome.

COMMENT

These are very condensed descriptions of the probable relationship between a slow tempo of neuromuscular maturation and the various aspects of the syndrome. Slow maturation appears to be the only factor that all the aspects have in common. From it, as has been shown, they all may be derived. It is argued that in fact they probably are so derived, and that therefore an inherited slow tempo of neuromuscular maturation is the fundamental cause of the syndrome.

This hypothesis in no way denies the importance of psychologic factors in stuttering, and of psychologic and educational factors in specific reading disability. It does suggest that they are not the primary cause. By revealing a common etiology for all the aspects of the syndrome it offers a reasonable explanation for their frequent association in the individual and in his family tree. It aids our understanding of the problem and gives us a simple explanation to present to the parents and to the children themselves.

It stresses the essentially developmental nature of the specific language disabilities and, therefore, should lead to their early treatment before faulty habits of speech and of reading have been firmly fixed by use. It suggests that for children of this type* reading should be postponed until the left-right direction of eye gaze is more firmly established, even though this may mean waiting until the second grade. When they do start to read, they should be taught phonetically and with kinesthetic reenforcement instead of by the "look and say" method.

*Children who were late in talking, are still rather ambidextrous, and lisp or stutter.

SUMMARY

A family tree covering four generations illustrates the familial nature of left-handedness and ambidexterity, bodily clumsiness, and the specific language disabilities. These conditions occur together in the individual and in his family tree sufficiently often to constitute a syndrome. The only factor that they appear to have in common is a slow tempo of neuromuscular maturation, which may be general or may be most conspicuous in certain skills. This slow maturation probably implies an equally slow tempo of myelination of motor and association nerve tracts. It is suggested that this inherited tendency to delayed neuromuscular maturation is the single factor from which all the various aspects of the syndrome may develop.

REFERENCES

1. Witty, P., and Kopel, D.: Reading and the Educative Process, Boston, 1939, Ginn and Company.
2. Blau, Abram: The Master Hand: Research Monographs No. 5, New York, 1946, American Orthopsychiatric Association, Inc. (These two contain excellent summaries and bibliographies.)
3. Berry, M. F.: The Developmental History of Stuttering Children, J. PEDIAT. 12: 209, 1938.
4. Nelson, S.: The Role of Heredity in Stuttering, J. PEDIAT. 14: 642, 1939.
5. West, R.: In Brennemann's Practice of Pediatrics, vol. IV, chap. 14, p. 25.
6. Orton, S. T.: Reading, Writing, and Speech Problems in Children, New York, 1937, W. W. Norton & Co.
7. Cobb, S.: Borderlands of Psychiatry, Cambridge, Mass., 1943, Harvard University Press.
8. Karlin, I. W., and Kennedy, L.: Delay in the Development of Speech, Am. J. Dis. Child. 51: 1138, 1936.
9. Langworthy, O. R.: Development of Behavior Patterns and Myelinization of the Nervous System in the Human Fetus and Infant, Contributions to Embryology, Carnegie Institution of Washington, vol. XXIV, No. 139, 1939.
10. Bremer, J. L.: Textbook of Histology, Philadelphia, 1936, P. Blakiston's Sons & Co.
11. Carleton, H. M.: Schaefer's Essentials of Histology, Philadelphia, 1938, Lea & Febiger.
12. Best, C. A., and Taylor, N. B.: The Physiologic Basis of Medical Practice, Baltimore, 1945, ed. 4, William & Wilkins Company.
13. Gesell, A.: In Brennemann's Practice of Pediatrics, vol. I, chap. 9.
14. McGraw, M. B.: The Neuromuscular Maturation of the Human Infant, 1943, Columbia University Press.

Case Reports

OMPHALOCELE WITH DIAPHRAGMATIC DEFECT AND HERNIATION OF THE LIVER INTO THE PERICARDIAL CAVITY

LIEUTENANT WALLACE W. MCCRORY, AND LIEUTENANT COLONEL ROLLIN F. BUNCH, MEDICAL CORPS, ARMY OF THE UNITED STATES

OMPHALOCELE is an uncommon developmental anomaly. The incidence of occurrence is reported to be one per 5,000 deliveries, and other congenital anomalies are found in one-third of this group.[1] We have recently observed two newborn infants with omphalocele who also had diaphragmatic defects with intrapericardial herniation of the liver and strikingly similar congenital cardiac defects. This unusual combination of congenital malformations prompts the following report.

CASE 1.—A full-term male infant was born spontaneously Sept. 15, 1946, with a birth weight of 6 pounds, 13 ounces. This was the first pregnancy of a 27-year-old white female. Maternal history was negative except for some vaginal bleeding in the second month of gestation. The infant was cyanotic at birth and only partial relief was afforded by continuous oxygen. A fairly large omphalocele (8 cm. × 6½ cm. × 2 cm.) was noted. The defect of the umbilical portion of the abdominal wall was covered only by a transparent membrane through which part of the liver, the omentum, and coils of small intestine were visible. The umbilical vessels coursed through this membrane. This saclike structure protruded above the adjacent abdominal wall. Physical examination of the chest revealed a loud, blowing systolic murmur heard over the entire precordium, loudest to the left of the sternum in the third and fourth intercostal spaces. No thrill was palpated. The lung fields were clear to auscultation and the remainder of the physical examination was otherwise negative. There were no other evident abnormalities. The omphalocele was dressed with penicillin ointment and petroleum jelly gauze. Penicillin was given parenterally 150,000 units daily. The infant was kept in an oxygen hood because of the dusky color and dyspnea. Surgery was postponed in anticipation of improvement in the patient's general condition. Approximately forty hours after birth the peritoneal fluid visualized through the omphalocele was opalescent and the infant's temperature had risen to 103.6° F. A complete blood count revealed a leucocytosis of 14,300 with 83 per cent neutrophiles, 12 per cent lymphocytes, and 5 per cent monocytes, 4,540,000 red blood cells with 14.4 Gm. hemoglobin. The serology was negative. It was felt that surgical repair of the defect was imperative at this time in spite of the cyanosis and dyspnea. The procedure was an extraperitoneal approximation of the normal skin edges over the defect. Postoperatively the infant was started on sulfadiazine in addition to penicillin, parenteral fluids were administered, and feedings were given by gavage because of the respiratory embarrassment. The infant's condition gradually became worse during the following week. There was no vomiting and the stools were normal. The temperature ranged from 99 to 103.8° F. The dyspnea steadily

From the Out-Patient Service and the Radiological Service, Walter Reed General Hospital, Washington.

increased, the heart tones grew distant, and the murmur became inaudible. The baby developed severe air-hunger during its eighth postoperative day and died on the ninth postoperative day.

The first x-ray taken the first day postnatally (Fig. 1) showed cardiac enlargement and a typical "Coeur en Sabot" deformity, suggestive of the tetrad of Fallot. There was an area of homogeneous increased density in the lower portion of the thorax with a smooth margin convex cephalically. It extended across the midline from the domes of the leaves of the diaphragm. The significance of this mass was not clear in spite of the elevation of the lower margin of the liver. Post mortem this mass proved to be the herniated superior surface of the right lobe of the liver. Later films showed only an increase in the size of the heart. Clinically we felt the infant had a severe congenital cardiac defect, probably a tetrad of Fallot. In view of the progressing evidence of cardiac failure we presumed congenital heart disease coupled with peritonitis to be the cause of death. The significant anatomic findings follow. The pericardium was normally formed except for the lower portion or floor. This was absent and the superior surface of the right lobe of the liver was protruding

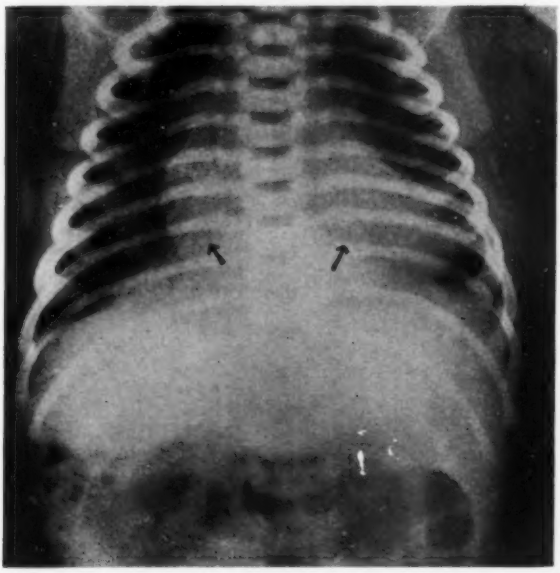


Fig. 1.—Case 1, with the typical "Coeur en Sabot" deformity of the heart, intrapericardial herniation of the liver (arrows) and elevation of the lower margin of the liver.

through the defect (Fig. 2). The apex of the heart was displaced to the left and upward by the liver. The pleural cavities were normally enclosed and the diaphragm and pericardium were without other defects. The ventral surface of the liver was adherent to the amnioperitoneal membrane. The falciform ligament fused with the inferior edges of the left lateral and posterior portions of the pericardial sac. The peritoneal cavity was thus closed dorsal to the falciform ligament but ventrally it was in free communication with the pericardial cavity. There was a rudimentary ledge ventrally where the portion of diaphragm that normally covers the dome of the liver and forms the pericardial

floor is attached to the abdominal wall. This shelf-like ridge constricted the liver tissue that was protruding into the pericardial cavity. The omphalocele extended to this rudimentary ledge, and hence the uppermost edge of the omphalocele was overlying the lower border of the pericardial cavity (Fig. 3). Dissection of the heart revealed a typical tetrad of Fallot, dextroposition of the aorta, interventricular septal defect, a bicuspid pulmonary valve and stenotic pulmonary conus, and hypertrophy of the right ventricle. The foramen ovale was functionally as well as anatomically patent. The ductus arteriosus was closed. There was an acute fibrinous pericarditis and peritonitis, and the pericardial cavity contained a moderate amount of fluid. No other abnormalities were found and the microscopic examination revealed no other additional pathology. The pericardial herniation of the liver produced the undefined mass seen in the x-rays. The increase in the size of the cardiac silhouette was not solely the result of congenital heart disease but was in part due to displacement by the liver and to the pericarditis with moderate effusion caused by the extension of the peritonitis through the pericardial-peritoneal communication.

Fig. 2.—Viscera of patient in Case 1 removed en bloc, viewed from above and anteriorly. The circular defect in the floor of the pericardium and diaphragm is shown. Herniated portion of liver is visible at lower margin of defect.

CASE 2.—A full-term male infant was born spontaneously Oct. 3, 1946. Birth weight was 6 pounds, 5 ounces. This was the second pregnancy of a 27-year-old white female. The maternal history was negative. Her first pregnancy was normal and the child is living and well. At birth an omphalocele similar to that in Case 1 was noted. The protrusion was greater than in the previous case. The defect measured 9 cm. × 7 cm. × 3 cm. The liver, omentum, and loops of small intestine were visible through the transparent covering of the defect. The infant was cyanotic without oxygen. Physical examination revealed a blowing systolic murmur heard over the precordium and to the right of the

sternum. The heart tones were loudest over and to the right of the sternum, suggesting the possibility of a dextrocardia. No thrill was palpated. The infant showed no other congenital abnormalities and the physical examination was otherwise negative. The defect was surgically repaired within four hours after birth to avoid peritonitis as occurred in our first case. The procedure was again extraperitoneal approximation of the normal skin edges of the defect. The baby did poorly postoperatively in spite of penicillin, sulfadiazine, parenteral fluids, oxygen, and gavage feedings. Respirations became progressively more irregular, shallow, and gasping. The temperature rose to 102.4° F. eight hours postoperatively. Twenty-four hours postoperatively the infant developed severe respiratory embarrassment following a gavage feeding. Auscultation of the lung fields, previously clear, revealed diffuse fine and coarse wet râles. The formula was reaspirated immediately after the feeding. Pharyngeal

Fig. 3.—Ventral aspect of viscera, Case 1. Superior margin of amnioperitoneal membrane at lower margin of pericardium and overlying intrapericardial portion of herniated liver. Constriction imprint on lower anterior surface of liver delineates portion herniated into omphalocele.

aspiration produced no improvement. Dyspnea rapidly increased and respirations ceased two hours later, thirty hours after birth. Laboratory studies showed a leucocyte count of 13,200 with 71 per cent neutrophiles, 23 per cent lymphocytes, 4 per cent monocytes, and 2 per cent eosinophiles, 5,300,000 red blood cells with a hemoglobin of 16.1 Gm. The serology was negative. The x-ray taken preoperatively showed an enlargement of the heart to the right which was attributed to either dextrocardia or displacement, the latter most probable since the apex appeared to be seen to the left of the sternum. The upper lobe of the right lung was atelectatic. The right leaf of the diaphragm was elevated and the inferior margin of the liver appeared to be displaced ventrally into the omphalocele (Figs. 4*A* and 4*B*). Clinically we felt this infant

had a serious congenital cardiac defect in addition to the omphalocele. Milk aspiration and atelectasis as a cause of death was considered. The post-mortem examination again demonstrated a diaphragmatic defect with absence of the pericardial floor in addition to the omphalocele. The defect was larger than in case one (Fig. 5, *A* and *B*). The only evidence of the falciform ligament was a cordlike strand that arose from the left lobe of the liver and fused with the inferior edge of the posterior pericardial sac. There was no rudimentary ledge ventrally where the ventral portion of the diaphragm normally attaches. The uppermost part of the amnioperitoneal membrane extended over the caudal part of the pericardial cavity. The anterior surface of the liver was adherent to this membrane and the liver was abnormally rotated. The "dome" of the liver was anterior; the right lobe was superior and extended into the pericardium, displacing the heart to the right and upward. The gallbladder was on the dorsal surface and the umbilical vessels were inserted into

Fig. 4*A*.—Case 2. X-ray shows collapsed upper lobe of right lung, cardiac displacement to the right, and elevation of the lower margin of the liver. Umbilical cord is visualized above right costophrenic angle.

the anterior surface. The pleural portions of the diaphragm were normal and free from any defects. Both lungs were markedly atelectatic, the lower lobes of both lungs were only partially expanded, the remainder nonair containing. The tracheobronchial tree contained no evident mucous plug and no milk or foreign matter. The heart showed multiple congenital defects: a patent foramen ovale and second interatrial septal defect, an interventricular septal defect, hypertrophy of the right ventricle, and a widely patent ductus arteriosus. There was no dextrocardia and the pulmonary valve and artery were apparently normal. There was no evidence of peritonitis and there were no other abnormal

findings. The microscopic examination revealed no additional abnormalities. In this case, the diaphragmatic defect and herniation of liver produced pronounced displacement of the heart to the right, but there was no x-ray evidence of intrathoracic herniation of the liver. The cardiac displacement due to the herniation of the liver and atelectasis simulated the picture of dextrocardia.

Fig. 4*B*.—Lateral view of patient in Case 2 showing omphalocele and ventral displacement of liver.

REVIEW OF THE LITERATURE

We were unable to find a descriptive report of a similar case in the American literature or mention of such a case in the larger series of omphalocele reported (O'Leary and Clymer,[1] ninety-one cases; Gross and Blodgett,[2] twenty-two cases; Specht and Shryock,[3] five cases; Stein and Gerber,[4] four cases; Jarcho,[5] and Margulies[6]). The occurrence of intrapericardial herniation of abdominal viscera in congenital diaphragmatic hernia not associated with omphalocele is most uncommon. One such case is reported by O'Brien.[7] Gross[8] reported a case with herniation of the liver into the pericardium that was successfully operated upon. Hedblom[9] in a review of all cases of diaphragmatic hernia reported up to 1924 listed the pericardium as the site of one herniation but did not describe the case. The larger series of case reports of congenital diaphragmatic hernia and reviews of this subject since 1912 make no mention of such defects (Harrington,[10] Hartzell,[11] Truesdale,[12] Orr and Neff,[13] Greenwald and

Steiner,[14] Ladd and Gross,[15] and Weinberg[16]). Sievers[17] reported a similar case of omphalocele with intrapericardial herniation of the liver in Germany in 1928 and reviewed other cases reported in the German literature.

Fig. 5A.—Case 2. Viscera removed en bloc, ventral aspect. Both lungs are atelectatic. Pericardium is reflected at upper margin of omphalocele.

DISCUSSION

There is considerable confusion in the literature in the definitive terminology of protrusive malformations of the umbilicus. Some of the synonyms are umbilical hernia, exomphalocele, exomphalos, hernia funiculi umbilicalis, ectopia viscerum, amniotic hernia, amniocele, and congenital eventration at the umbilicus. The present trend is toward simplification of the nomenclature, using the terms omphalocele, hernia into the cord, and congenital umbilical hernia to classify the defects encountered. As defined by Margulies[6] "Omphalocele should apply to the anatomical and formational entity involving the supraumbilical and umbilical portion of the abdominal wall, to differentiate it from a hernia into the cord, in which loops of intestine, liver, or omentum protrude through a small ring into the cord and from true umbilical hernia covered by skin."

The embryologic mechanism responsible for omphalocele is still indefinite. By some the assumption is that the defect results from the failure of the organ contents of the umbilical sac to withdraw into the celomic cavity at about the third month of fetal life, thus preventing the normal formation of the umbilicus (O'Leary and Clymer,[1] and Jarcho[5]). Others feel that retarded development of the abdominal parities may give rise to a disparity between the size of the abdominal viscera and the abdominal cavity (Gross and Blodgett,[2] Specht and Shryock[3]). In his excellent discussion of the subject, Margulies[6] revives interest in the possible significance of faulty growth of the primitive septum transversum as a causative factor in the production of omphalocele. He cited the work of German embryologists on the development of the ventral body wall. According

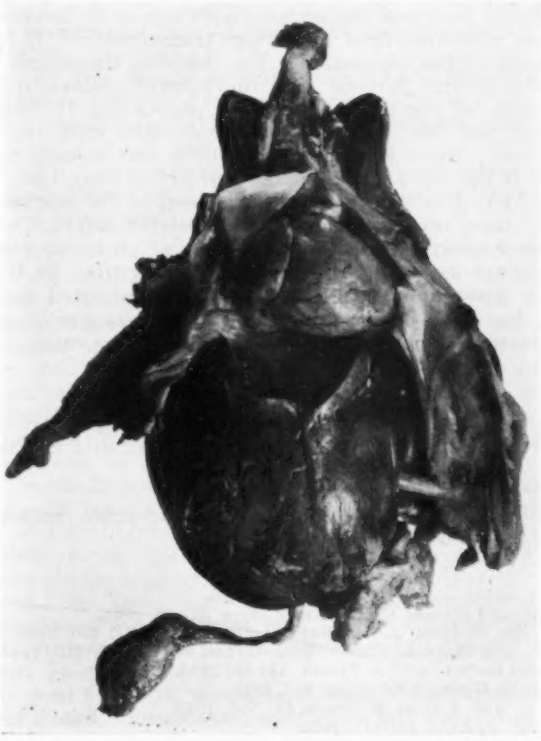


Fig 5*B*.—Case 2. Viscera with pericardium and amnioperitoneal membrane reflected. Defect in floor of pericardium and diaphragm is shown. Imprint of the heart is visible on liver surface.

to these authors, the supraumbilical part of the abdominal wall has a transient covering of amnion. This is normally moved caudad to the umbilical cord by the growth of liver cells into and connective tissue from the septum transversum. In this way it gives rise to the supraumbilical portion of the abdominal wall. This process is dependent on the concrescence of the amniotic covering and the tissues of the septum transversum. Failure of such union or of proliferation of the connective tissue from the septum transversum would allow persistence

of an amnion covered gap, and the result is an amniocele (omphalocele). These processes are completed by the third week of fetal life, while the withdrawal of the abdominal contents from the extracelomic cavity normally occurs in the eighth to tenth week. Margulies thus concludes that failure of the withdrawal of the abdominal contents of the umbilical sac cannot produce an omphalocele, but rather results in a true hernia into the cord.

Sievers[17] in his report of a case similar to ours, states that omphalocele is probably related to faulty development of the septum transversum with a consequent deficiency in the supraumbilical portions of the abdominal wall. He discusses other cases of omphalocele associated with pericardial-diaphragmatic defects of varying degree, some so extensive that the heart was found lying in the peritoneal cavity.

The pericardial floor and contiguous diaphragm and the ventral diaphragmatic attachment is derived from the septum transversum.[18] It forms the later centrum tendinum of the diaphragm. The complete diaphragm is formed by the fusion of the pleural portions with this central portion in a complicated manner.[18] In both of our cases the pleural portions of the diaphragm were normally formed and free from any communications with the peritoneal or pericardial cavities. Since the defects present in our cases involved only the central portion of the diaphragm and the pericardial floor, these could well be the result of a local deficiency in the development of the septum transversum.

We present these two cases with their associated defects for their clinical and embryologic interest. The successful repair of an intrapericardial herniation of the liver not associated with omphalocele reported by Gross[8] indicates that this defect is not incompatible with life. The reported mortality rate in omphalocele is less than 50 per cent. The severe congenital cardiac defects present in our two patients were probably the major cause of death.

SUMMARY

1. Two cases of omphalocele with absence of the pericardial floor, intrapericardial herniation of the liver and severe congenital cardiac defects are reported.

2. The literature on the subject is reviewed.

3. The embryologic explanations of the mechanism responsible for the development of omphalocele are discussed.

REFERENCES

1. O'Leary, C. M., and Clymer, C. E.: Am. J. Surg. **52**: 38, 1941.
2. Gross, R. E., and Blodgett, J. B.: Surg. Gynec. & Obst. **71**: 520, 1940.
3. Specht, N. W., and Shryock, E. H.: Surg. Gynec. & Obst. **77**: 319, 1943.
4. Stein, J. L., and Gerber, A.: J. PEDIAT. **14**: 89, 1939.
5. Jarcho, J.: Surg. Gynec. & Obst. **65**: 593, 1937.
6. Margulies, L.: Am. J. Obst. & Gynec. **49**: 695, 1945.
7. O'Brien, H. D.: J. Anat. **74**: 131, 1939.
8. Gross, R. E.: Am. J. Dis. Child. **71**: 579, 1946.
9. Hedblom, C. A.: J. A. M. A. **85**: 947, 1926.
10. Harrington, S. W.: Ann. Surg. **115**: 705, 1942.
11. Hartzell, J. B.: Am. J. Surg. **48**: 582, 1940.
12. Truesdale, P. E.: New England J. Med. **213**: 1159, 1935.
13. Orr, T., and Neff, F. C.: J. Thoracic Surg. **5**: 434, 1936.
14. Greenwald, H. M., and Steiner, M.: Am. J. Dis. Child. **38**: 361, 1929.
15. Ladd, W. E., and Gross, R. E.: New England J. Med. **223**: 917, 1940.
16. Weinberg, J.: Surg. Gynec. and Obst. **72**: 445, 1941.
17. Sievers, R.: Arch. f. klin. Chir. **153**: 703, 1928.
18. Bremer, J. L.: Arch. Path. **36**: 539, 1943.

SCLEREMA ADIPOSUM NEONATORUM

ALBERT STERNBACH, M.D., AND JOSEPH ROBINSON, M.D.
BROOKLYN, N. Y.

SCLEREMA adiposum neonatorum is a disease of the first few weeks of life, characterized by widespread, patchy hardening of the subcutaneous tissue, the etiology of which is unknown. Infants suffering from this illness are usually premature, exhibit subnormal temperature, apathy, poor feeding and inability to gain weight resulting in rapid malnutrition and dehydration, and terminating in death within a few weeks.

Pathologically, this disease is characterized by a foreign-body granuloma showing wide fibrous branching trabeculae, neutral fat crystals, numerous proliferating blood vessels, and infiltration by foreign-body giant cells, lymphocytes, and an occasional polymorphonuclear leucocyte.

Since this entity is uncommon and because of close observation of a patient with a prolonged clinical course, including post-mortem examination, we are reporting the following case.

CASE REPORT

History.—A white male infant was born Sept. 11, 1946, to a 35-year-old mother who had a history of eight previous pregnancies including one abortion at the third month of gestation. The present pregnancy was full term and complicated by mild pre-eclampsia. Birth was spontaneous and the amniotic fluid was meconium-tinged. The mother's Wassermann was negative.

Clinical Examination.—The infant weighed 11 lbs., 8 ozs., and measured 21.5 inches. Scalp ecchymosis and moderate signs of moulding with overriding of the parietal bones, as well as marked caput at the vertex were present. The anterior fontanelle was not bulging. Supra- and infrasternal retraction were noted. Breath sounds were vesicular and transmitted throughout; heart tones were of good quality without murmurs; cry and color were fair. Sixteen hours after birth, clonic seizures of facial and arm muscles were present. Vitamin K and calcium gluconate therapy were administered.

On the second day, facial tremors and moderate spasticity of all extremities with marked flexion of the left wrist were noted. Cyanosis and regurgitation were prevalent, but responded to oxygen inhalation and gavage. A 16 oz. weight loss was present since birth.

During the next few days, several new features developed, such as cephalic cry, thrush, and a hard, subcutaneous mass in the left arm. A clysis of Lactate-Ringer's solution was ordered and the monilia infection cleared rapidly with 1 per cent aqueous gentian violet applied topically. A scalp infection followed, with several areas of oozing. A dry gangrenous slough developed in the occipital area, despite 10,000 units of penicillin every three hours intramuscularly and a 60 c.c. transfusion of whole blood. A low-grade fever and cyanosis persisted, but feeding definitely improved.

On September 22, several firm, indurated, subcutaneous areas were noted on the cheeks, back, volar surfaces of arms, calves, and abdomen. The flexion deformity of the left wrist had decreased since application of splints and the scalp was healing rapidly. A blood count showed 20,000 white blood cells

From the Departments of Pediatrics and Pathology, Kings County Hospital (Kings County Division) G. C. Brockway, M.D. and C. G. Burn, M.D., Directors of Services.

per cubic millimeter, polymorphonuclears 70 per cent, lymphocytes 30 per cent, hemoglobin 14.5 Gm., and 4.8 million red blood cells.

X-ray examination at this time revealed moderate separation of all intracranial sutures, particularly in the basiocciput with no evidence of bony involvement of the upper extremities. No pulmonary pathology was evident.

A subdural tap was performed bilaterally but bloody fluid was not obtained. A spinal tap between the second and third lumbar vertebrae was unsuccessful. A cisternal puncture revealed clear, colorless, spinal fluid containing 5 lymphocytes per cubic millimeter, protein 74 mg. per cent, sugar 65 mg. per cent, with negative serology and colloidal gold, and which was sterile on culture.

Orthopedic consultation noted a "spastic contraction of all fingers of the left hand, with thumb markedly adducted and the wrist markedly flexed. The right hand is in flexion but extension of the fingers and wrist does occur.

Fig. 1.—Section through entire thickness of skin and subcutaneous tissue. Note "nodular" pattern.

Diagnosis.—Cerebrospastic with flexion contracture of both wrists, more marked on left.

On October 22, a biopsy of one of the indurated areas on the calf was performed. The specimen consisted of skin and subcutaneous tissue which was moderately firm and white. The microscopic section of skin and subcutaneous tissue showed intact epidermis with normal morphology. The subcutaneous fat layer was traversed by thick, fibrous, collagenous trabeculae and areas of looser connective tissue, throughout which were numerous foreign-body giant cells containing from 5 to 30 nuclei. The diagnosis was sclerema adiposum neonatorum.

The infant began to vomit again and rapidly developed signs of dehydration. A pinhead-sized draining sinus was noted over the lesion of the left forearm. Subcutaneous clyses were administered. At this time the hemoglobin was 12.5

Gm. per cent, 4.2 million red blood cells, hematocrit 36.5 per cent and plasma proteins 5.5 gm. per cent. Urinalysis revealed an acid reaction, albumin one plus, sugar negative, microscopic negative, and Sulkowitch test was positive for calcium.

Since vomiting persisted despite formula changes consisting of Sobee and thickened cereal feedings with and without atropine, a gastrointestinal series seemed advisable. The x-ray report follows:

"Fractional study of the gastrointestinal tract within a period of five hours shows no intrinsic lesion visible in the stomach or duodenum. A slight delay of gastric evacuation is noted within three hours. In five hours most of the barium is distributed in the lower portion of the small intestine with a small gastric residue."

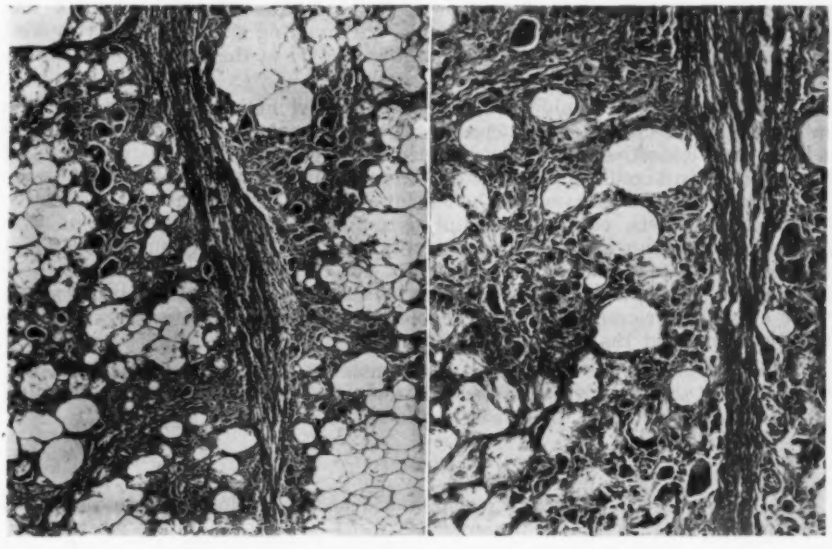


Fig. 2. Fig. 3.

Fig. 2.—Section through skin and subcutaneous tissue; stained with H. & E. (×100). Note thickening and branching of fibrous trabeculae and numerous foreign-body giant cells.

Fig. 3.—Same section as Fig. 2 with higher magnification (×440).

Vomiting and dehydration continued despite subcutaneous clyses and small blood and plasma transfusions. Diarrhea ensued, for which oral feedings were stopped and continuous intravenous fluids were given, including parenteral vitamin therapy. The diarrhea abated but a subnormal temperature occurred and was followed by coma and generalized fine inspiratory rales. A blood CO_2 combining power was 30 volumes per cent and urea 69 mg. per cent. The baby expired Nov. 14, 1946, sixty-four days following birth.

NECROPSY

At necropsy, twenty-one hours after death, the body was that of a white, 2-month-old male infant, measuring 22 inches and weighing approximately 12 lb. Several large, firm, subcutaneous, fibrotic patches were palpated, which were most marked on both cheeks, buttocks, thighs, right lower deltoid, flexion

surfaces of the forearms, and both calves. The thyroid was not palpable. The abdomen was moderately distended. Both testes were descended. The adipose tissue measured 3 mm. over the thorax and 6 mm. over the abdomen. The superficial layer was firm and divided into numerous distinct grayish brown lobules beneath which a deeper layer of white, gelatinous, transparent, glistening fat was noted. Many cutaneous nerves were distinctly seen within this portion of skin.

The peritoneal cavity contained about 100 c.c. of clear, straw-colored fluid with a few fibrin flakes. The stomach was moderately distended; the intestines were collapsed. The liver extended 4 cm. beneath the right costal margin in the midclavicular line, 1 cm. beneath the xiphoid process, and the left border was at the left costal margin in the midclavicular line. The urinary bladder was distended. The kidneys and ureters were in their usual position. The thoracic and abdominal cavities showed nothing unusual. The thymus was small and contained a moderate amount of surrounding fat. The brain showed an area of softening measuring 1 x 1 cm. in the gyri of the right temporal area just beneath the cortex.

Histologically, the epidermis and cutis showed normal morphology. The subcutaneous fat revealed numerous branching trabeculae composed of dense collagenous connective tissue, the borders of which were lined by young fibroblasts and giant cells and contained large proliferating blood vessels, some obliterated. At the junction of the subcutis and fat, there was a thin reactive band of fibroblasts, occasional lymphocytes and polymorphonuclears as well as numerous foreign-body giant cells containing five to thirty nuclei. Special fat stain (Sudan III) showed numerous neutral fat crystal in the adipose layer. When examined with a polarizing microscope, using crossed Nicol prisms, these crystals were seen to rotate the plane of polarized light and shined brilliantly throughout the section.

Microscopic examination of all the remaining organs revealed normal histology except the liver, which showed hydropic degeneration and cloudy swelling of the parenchyma with distention of the sinusoids.

COMMENT

A review of the literature reveals a marked confusion between the terms sclerema, pseudosclerema, and scleredema, which many authors use interchangeably. This concept is erroneous since each can be differentiated clinically and pathologically.

Sclerema is characterized by:

1. Onset: within the first two weeks of life.
2. Distribution of lesions: Parts with most fat involved such as cheeks, buttocks, back and extremities (thighs, calves, and forearms). The lesions of the extremities tend to follow the long axis.
3. Palpation: discrete, nontender, nonfluctuant, nonpitting, firm, indurated lesions, with irregular borders. The skin is not movable over the lesion.
4. Color: prevailing tint of skin.
5. Course of lesions: no regression or calcification; possible ulceration.
6. Systemic effects: subnormal temperature, gastrointestinal upset, dehydration, debility, and death after several weeks or months.

Pseudosclerema, or subcutaneous fat necrosis, is usually traumatic in origin with no uniform distribution, occurring at any age, without systemic effects, and characterized locally by tenderness, an overlying, freely movable skin,

with or without discoloration or ulceration. This is a benign condition which usually resolves; occasionally calcification results.

Scleredema (infantile) or edema neonatorum, is a particular variety of edema in which the skin is very hard but exhibits pitting, and is not adherent to the underlying subcutaneous tissue. The parts involved are usually the feet, calves, outer thighs, but occasionally the genitals and palms and soles are affected. These latter sites are always spared in sclerema adiposum.

Biopsy conclusively establishes the diagnosis.

The etiology of sclerema adiposum neonatorum is unknown, although many theories have been proposed. The most widely accepted explanation is that a deficiency of unsaturated fat exists in the adipose tissue, thereby causing it to solidify at a higher temperature than is needed for normal fat. This results in a foreign-body reaction of the tissues.

Although the literature emphasizes the prevalence of this disease in premature infants with an extremely rapid course (two to three weeks); the above case, on the contrary, is that of a large baby with a protracted illness.

SUMMARY

A case of sclerema adiposum neonatorum is presented, including necropsy. The terminology, etiology and differential diagnosis is discussed. Unlike most cases, this patient was unusually large and pursued a prolonged clinical course.

REFERENCES

1. Zeep and Madden: Arch. Path. **41**: 166, 1946.
2. Reich: Arch. Derm. & Syph. **45**: 342, 1942.
3. Miller and Kritzler: Arch. Derm. & Syph. **47**: 82, 1943.
4. Fox: Arch. Derm. & Syph. **27**: 237, 1933.
5. Spain and Foley: Am. J. Path. **20**: 783, 1944.
6. Wells: J. A. M. A. **114**: 2177, 1940.
7. Brennerman: Text. Practice of Pediatrics **19**: 1, 1947.
8. Holt and McIntosh: Text. Dis. of Infancy and Childhood **876**: 11, 1939.

ADENOLEIOMYOFIBROMA OF THE TONGUE

Report of a Case in an Infant

Eugene L. Slotkowski, M.D., and Maxwell P. Borovsky, M.D.
Chicago, Ill.

TUMORS of the tongue in early infancy are very uncommon and are usually cystic in origin. Most of these cysts are formed from the retention of secretions in one of the numerous mucous glands present in the tongue and usually appear near the lingual base. They may produce stridor, dyspnea, difficulty in deglutition, and cyanosis. Pressure of the tumor against the epiglottis may completely occlude the laryngeal orifice and result in asphyxia.[1, 2]

A thyroglossal cyst at the base of the tongue is located in the midline and results from incomplete obliteration of the thyroglossal duct. It may not appear or produce symptoms until adult life.

Ranulae are acquired or congenital retention cysts of the salivary ducts or mucous glands in the floor of the mouth. They may reach the size of a plum at the time of birth[3] and surgical intervention (aspiration of the contents) is necessary to reduce the size of the mass which interferes with the mobility of the tongue and coordinated deglutition. Some ranulae can be completely excised, because they involve glands which have no connection with the salivary group.

The descent of the thyroid gland may be arrested at any point between the foramen cecum and its normal destination, with the tongue being one of the aberrant locations of this gland. Montgomery,[4] in his comprehensive review of lingual thyroid, lists several cases of this condition found in infants at autopsy, one of them in the newborn period. It is not clear whether the lingual thyroid contributed or was the cause of death in these instances.

Glandular tumors of the tongue in infants are exceedingly rare. Hickman, in 1869, reported a case which occurred in a newborn infant and caused suffocation sixteen hours after birth with the tumor mass extending from circumvallate papillae nearly back to the epiglottis. Pattie[5] reported a case of a 3-month-old infant with difficulty in feeding, regurgitation of food, choking, dyspnea and cyanosis. The mass was first noticed by the mother while the infant was crying. A pedunculated tumor (2 x 1.5 x 1 cm.) was found to be attached in the midline near the base of the tongue. Microscopic section revealed normal mucous glands surrounded by tongue muscle fibers, fibrous and adipose tissue.

CASE REPORT

F. S., a 9-month-old Negro female infant, was admitted to the Children's Division of Cook County Hospital on Feb. 2, 1947. The mother stated that several days prior to admission she noticed a small ball-shaped structure in the patient's mouth which flipped up from the base of the tongue when the infant cried. Prior to that time it had not been noticed. The infant never had any difficulty in deglutition or respiration. Except for a rash on the scalp the patient had been in good health.

The physical examination revealed a well-developed, well-nourished, Negro female child who did not appear ill. A small number of crusted papules covered the face and cheeks. Inspection of the pharynx disclosed a fleshy, smooth,

From the Children's Division of Cook County Hospital.

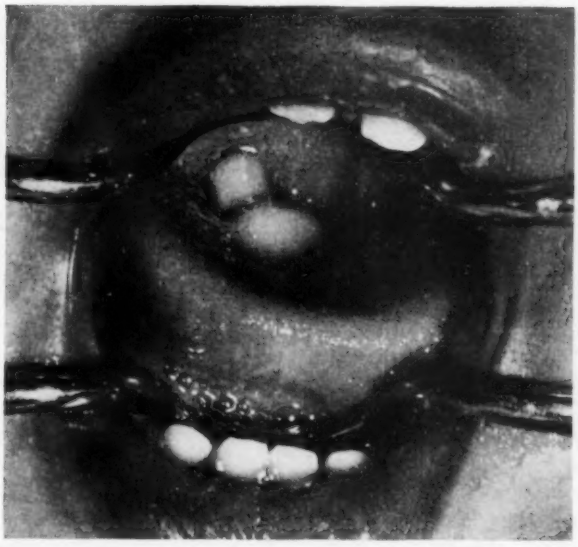


Fig. 1.—Tumor mass visualized during coughing spell. Jaws separated by means of mouth gag.

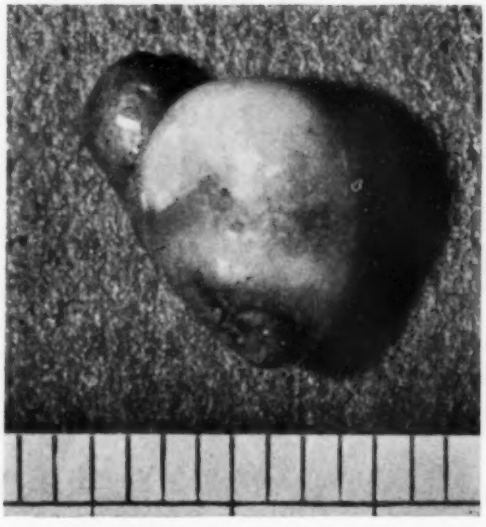


Fig. 2.—Appearance of mass shortly after removal by snare and electrocoagulation of base.

Fig. 3.

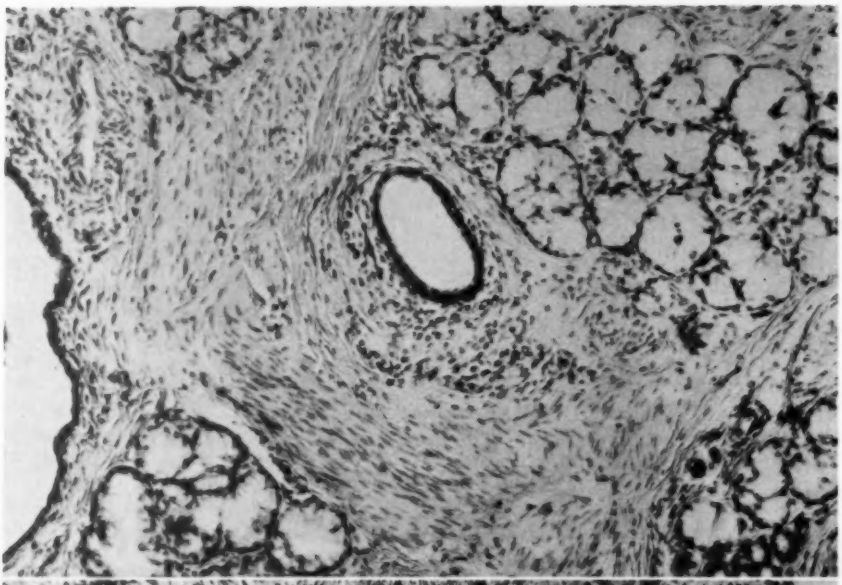


Fig. 4.

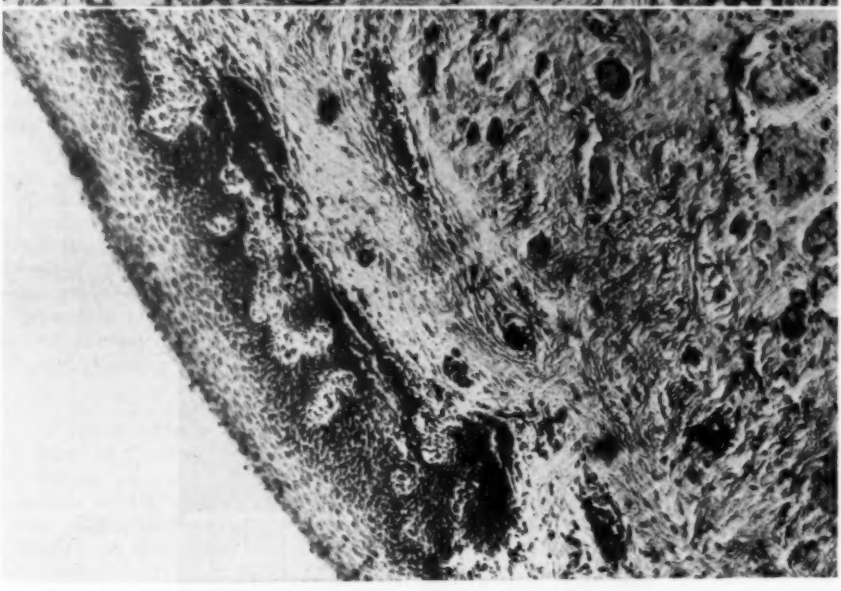


Fig. 3.—Photomicrograph under low power magnification showing nests of mucous glands, dilated ducts, muscle fibers, and connective tissue.

Fig. 4.—Photomicrograph of periphery of nodule under low power magnification showing stratified squamous epithelium and lymphocytic infiltration in submucosa.

polypoid mass about 1.5 cm. in diameter and attached by a pedicle to the base of the tongue in the midline, popping into the oral cavity (Fig. 1) upon gagging the patient. On palpation the mass felt firm in consistency.

During the period of hospitalization prior to surgery the infant did not manifest any obstructive symptoms. Several days after admission the tumor (Fig. 2) was removed by snare and electrocoagulation of base.

Macroscopically, the specimen consisted of well-encapsulated somewhat lobulated firm tissue. The nodule was light brownish gray in color and measured 1.5 x 1 x 0.8 cm. On section it appeared grayish white to pale yellow-gray.

On microscopic examination, numerous nests of mucus-secreting glands lying adjacent to dilated ducts were observed. These groups of mucous glands were widely separated by underlying bundles of smooth muscle fibers and small bands of fibrous connective tissue (Fig. 3). In the periphery of the nodule, a greater amount of fibrous connective tissue containing small bundles of smooth muscle fibers was found. The tissue adjacent to the mucous membrane which was composed of stratified squamous epithelium showed foci of lymphocytic infiltration particularly about the dilated capillaries in the papillary layer of submucosa (Fig. 4).

DISCUSSION

The tumor mass did not cause any respiratory embarrassment or difficulty in deglutition, even though its size was such that it could have blocked the glottic opening either partially or completely. It is interesting to note that the tumor was located in the midline, attached to the base of the tongue in the area of the foramen cecum. Under those conditions the anatomic relationship normally found would place the epiglottis between the tumor mass and the larynx with the epiglottis acting as a protecting shield, preventing the blocking of the laryngeal orifice. In this respect, the epiglottis has been aptly named by Jackson[6] as the "watchman of the larynx."

SUMMARY

An unusual glandular tumor of the tongue is reported. Although located at the base and attached near the foramen cecum, it did not cause any difficulty in deglutition or respiration. The anatomic relationship of the epiglottis to the tumor mass may be the possible explanation for the lack of symptoms.

Surgical removal of the tumor was performed by Dr. M. Cottle of the Ear, Nose and Throat Department. Gross specimen and microscopic sections examined by Dr. A. Ragins of Surgical Pathology.

REFERENCES

1. Leuw, K.: J. A. M. A. 83: 1957, 1924.
2. Whittier, L., and Dombrowsky, E. F.: J. PEDIAT. 29: 774, 1946.
3. Personal Observation.
4. Montgomery, M. L.: West. J. Surg. 43: 661, 1935; 44: 54, 122, 189, 237, 303, 1936.
5. Pattee, G. L.: Colorado Med. 32: 718, 1935.
6. Jackson, C., and Coates, G.: The Nose, Throat and Ear and Their Diseases, Philadelphia and London, 1930, W. B. Saunders Company, p. 738.

SALMONELLA CARRIER TREATED SUCCESSFULLY WITH STREPTOMYCIN

HELEN E. SWILLER, M.D., A. IRVING SWILLER, M.D., AND FREDERICK B. TRAUB, M.D.,
BROOKLYN, N. Y.

THE problem of the carrier state in Salmonella infections has always been of interest, especially from the epidemiologic viewpoint, and it is for this reason that the following case is reported.

On Sept. 23, 1946, an 8-month-old white male infant suddenly developed profuse watery diarrhea, passing twenty stools in the first twenty-four hours, the temperature rising to 103.8° F. Examination revealed a rather pale, acutely ill infant; skin was hot and dry, turgor fair, and the fontanelle was not depressed. Examination was otherwise negative and no obvious cause was found to account for the fever and diarrhea. Two weeks prior to this onset, the child had had an acute nasopharyngitis with a febrile rise for which he was treated with sulfadiazine, and the infection subsided in forty-eight hours. His past history was otherwise negative.

The child was treated by withholding all food for ten hours meanwhile giving fluids ad lib and sulfadiazine gr. 1 per pound of body weight per twenty-four-hour period in doses every four hours. With some subsidence of the diarrhea, boiled skimmed milk, gelatin, and banana were gradually introduced. His stools became reduced in number, eight to ten daily, and smaller in size, consisting mainly of jellylike globs of mucus mixed with small amounts of blood. His temperature gradually subsided to 100.6° F. and then fluctuated between 100.6 and 101° F. On the fourth day, the spleen became palpable two fingerbreadths below the subcostal margin, and a cluster of small pink papules were seen scattered over the right side of the abdomen. A solitary lesion on his chin appeared very much like a "rose spot" of typhoid.

On September 28, the stool was cultured for pathogens, and organisms of Salmonella Group C_2 were isolated and later identified as *Salmonella newport*. Sulfasuxidine was started in doses of 5 grain per pound of body weight per twenty-four hour period, divided into equal doses every six hours. Bowel movements continued six to eight daily and consisted of partially digested food admixed with glary mucus. Blood which had been invariably present disappeared from the stool after the first day on sulfasuxidine. Sulfasuxidine was continued for three weeks, the temperature gradually subsided to normal after one week, and the bowel movements returnd to a normal consistency, three to five stools daily with less mucus. The spleen remained palpable for three months. Rectal swabs were cultured every other day during this period and thereafter and were invariably positive for Salmonella.

At no time did anyone else with whom he was in close contact show a positive culture and the source of his infection was never ascertained. Inasmuch as positive cultures were invariable, and although the child was clinically well, for public health reasons he was kept apart from other children. It was finally decided to try to rid his bowel of the organism by the use of streptomycin orally. A sensitivity to this antibiotic was determined in vitro and it was found that ten units of streptomycin per milliliter of medium inhibited the growth of the organisms.

On Jan. 14, 1947, four months after the onset, the infant was started on streptomycin, one gram daily (one million units) given orally in three equally divided doses. The streptomycin was dissolved in 5 c.c. of distilled water, yielding a solution of 6 c.c., and the patient was given 2 c.c. in fruit juice

From the Jewish Hospital of Brooklyn.

three times daily after meals. (It might be noted that the taste was apparently in no way objectionable and that the child did not even detect its presence.) After the administration of one gram of streptomycin, stool culture was found to be completely sterile, with no *Bacillus coli* and no Salmonella. Stools remained sterile and also odorless throughout the twenty days of treatment and for two days thereafter. During this time the stool was of soft consistency. On the third day after the administration of the streptomycin was stopped, *B. coli* began to appear in the cultures and all cultures taken every other day for a period of six weeks subsequently have shown a rich flora of *B. coli* and absent Salmonella.

Bacteriology.—Material for bacteriologic examination was obtained by swabbing the rectum with a sterile cotton applicator. In addition, during and after the administration of streptomycin, fresh specimens of stool were also collected.

The swabs were plated on SS and MacConkey agar plates and incubated for eighteen to twenty-four hours. Stool specimens were cultured in the Kauffmann's tetrathionate enrichment broth for eighteen hours and then subcultured on MacConkey agar plates. Colorless colonies from SS or MacConkey agar were subcultured into liquid sugar media and examined for motility and indole production. A twenty-four-hour broth culture grown at room temperature was used for serologic tests. The organism was identified by specific O and H sera as *Salmonella newport*. We are indebted to Dr. E. Seligmann of the National Salmonella Center of New York for these sera. On two occasions cultures of the organism were sent to Dr. Seligmann and the presence of *Salmonella newport* was confirmed by him.

COMMENT

Inasmuch as the organism was always present, even after the administration of the sulfadiazine and later sulfasuxidine, although there was clinical improvement after the latter, we do not feel that the sulfasuxidine exerted any beneficial effect on the course of the disease. We rather feel that the acute phase had coincidentally ended and that the disease had entered the carrier phase. The prompt sterilization of the stool after the administration of the oral streptomycin, however, cannot, in our opinion, be a mere coincidence. The streptomycin was given orally in order to obtain local action in the bowel. It is known that this antibiotic is not appreciably absorbed from the gastrointestinal tract and hence large doses could be given without fear of toxicity. While this paper was being prepared for publication, Seligmann and associates* reported a complete failure of elimination of *Salmonella typhimurium* from the stool of a series of cases of infants. It might be important, therefore, to point out the differences between their series and our case. Seligmann and co-workers were dealing with the acute stage of the infection, while we were treating a carrier. Furthermore, they were using much smaller doses and over a shorter period of time. Although we make no pretense to draw conclusions from a cure in one case we feel that it is worth reporting, since it seems to point the way to an efficient treatment of Salmonella carriers.

SUMMARY

An infant in the carrier state of Salmonella infection was successfully treated with streptomycin administered in large doses orally over a prolonged period of time.

We are extremely grateful to the Charles Pfizer Co., through whose kindness the streptomycin was supplied.

*Erich Seligmann, M.D., Louis Barash, M.D., and Sidney Cohlan, M.D. Streptomycin Treatment of Salmonella Enteritis in Infants, J. PEDIAT. 30: 182, 1947.

The Social Aspects of Medicine

On the Taft Bill

July 22, 1947

Dear Dr. Park,

Senate Bill 545, National Health Act of 1947, commonly called the "Taft Bill," was introduced in the Senate Feb. 10, 1947, and has been under discussion by many medical groups, both at the hearings in Washington and in various publications. The bill is evidently offered as a substitute for the Wagner Bill, a new draft of which was introduced in the Senate May 20, 1947. In comparing the two bills, one cannot fail to be impressed by the careful, logical treatment of the subject of medical care in the Wagner Bill and the inadequate and uncomprehending approach of the Taft Bill. The objection to the Wagner Bill on the part of those who do not support it, and I am one, is that it is dependent for its operation on compulsory health insurance. If it were not for this feature, the bill, with certain modifications, could be indorsed. Assuming sincerity of motive in the sponsors of the Taft Bill, does it present a satisfactory approach to the solution of the problem of improving medical care in this country without the objectionable feature of compulsory insurance? I do not think so, as it does not provide a plan which offers any likelihood of modifying medical care procedures so that the benefits of medical science may be available to all the people.

It is not necessary here to analyze the bill in detail; this has been done in publications of the American Medical Association, the American Public Health Association, The Physicians' Forum, and The Committee of Physicians for the Improvement of Medical Care. It may be worth while to point out some of the reasons why the Taft Bill is unsatisfactory.

The bill sets up the National Health Agency in the executive branch of the Government. The agency will take over the Public Health Service, The Children's Bureau, the Food and Drug Administration, and add two new Divisions, Medical and Hospital Care Services and Dental Care Services, and the Administrator, who is appointed by the President, with the advice and consent of the Senate. He must be a physician "outstanding in the field of medicine," but nothing is said about either his qualifications in administrative responsibility or his background in public health knowledge or practice. There are several fields from which an able administrator might be selected; private practice could produce such an individual, but it is not the most likely group in which to find him.

Already real progress has been made in the consolidation and coordination of the various health services of the Government under the Social Security Administration. This is a step toward bringing together health, education, and welfare into a department with its head a member of the cabinet. The Taft Bill scraps all this advance, and the proposed agency would have no cabinet representative but would report directly to the President. This is not in line with good administrative practice.

Title VII, Medical and Hospital Care Services, is the portion of the bill dealing directly with the problems of most interest to physicians. The administrator of these services must be a physician "who has had at least five years

of active medical practice." Again it should be pointed out that this in no way guarantees the appointment of a person with administrative ability and vision. It smacks of control by organized medicine and a stand-pat outlook.

Nowhere is there any provision at the Federal level to assure quality of the services rendered. It is fantastic to pass out money from the Federal Treasury without any assurance that there is even a reasonable chance that it will not be wasted. A provision safeguarding quality of service need not carry with it bureaucratic control of details nor dictation with respect to appointments of personnel. Failure to include such a provision invites waste and incompetence.

The advisory council is too heavily weighted with medical personnel and the general public too scantily represented. The provision that the advisory council can override the administrator in approval of State plans is not good administrative practice.

Another fault in the bill is its coverage. It is stated that the design is to assist "families and individuals of low income;" no statement of whom this includes is given and no provision is made for the families of moderate means, who need assistance most of all. Those who receive medical care on a charity basis fare very well at the present time; it is the families above that economic level who want good medical care but are unable to bear the costs without some assistance from the Government. The bill does not meet their need. The application of the means test is cumbersome and very difficult; even at the local level, where some workable plan might be devised, the bill does not provide the answer. Appropriations to meet the costs of service, after the first five years will be granted from year to year according to the whim of the Congress, and the "low income" group might easily fall lower and lower. There is no assurance of stability in the plan.

Altogether, the bill fails to present a carefully conceived or intelligently planned national health service. Surely something better than this can be provided; if not, then compulsory insurance along the lines proposed in the Wagner-Murray Bill will surely be enacted.

RICHARD M. SMITH, M.D.

CHILD WELFARE IN BRITAIN

ALAN MONCRIEFF, F.R.C.P.*
LONDON, ENG.

Just over a hundred years ago the public conscience in Great Britain began to be stirred about matters of health. Several national epidemics, cholera for example, had given rise to great alarm. Experienced medical practitioners attributed such epidemics to the deplorable conditions under which many of the poor in great cities lived and worked. A special Act of Parliament in 1836 set up a system for registering the exact cause of all deaths. Three years later, a doctor began a series of annual reports on the nation's health, based for the first time upon accurate facts and figures.

A study of these reports soon revealed that the annual death roll was appallingly high among babies and women in childbirth. Important steps were taken to improve the midwifery services, and the later years of the Nineteenth Century saw also the beginning of organized efforts to deal with disease and death among infants and young children.

Two main causes of child deaths were obvious, ignorance and dirt. The remedies were to educate mothers in the management of their babies, and to

*Director of the Institute of Child Health; Nuffield Professor of Child Health, University of London.

A broadcast over BBC.

provide a clean and safe supply of milk and infant food when breast feeding was not available. The earliest organized effort in Britain at child care for the very young dates from 1890 when the City of Manchester established a "welfare service" which provided for women with some elementary training in hygiene to call at the homes of mothers to help them in caring for their babies and teach them the rudiments of infant hygiene. A few years later Britain's first "Infant Milk Depot" was started. Here milk could be obtained which was free from dangerous germs.

The subsequent development of child welfare in Britain has followed these two main lines. Some of the earliest welfare clinics were called "Schools for Mothers," and mothers were encouraged to attend regularly for instruction, for the progress of their infants to be watched, and to have the child medically examined so that incipient disease could be detected before it became serious. At such clinics milk and milk-foods were available. Home visiting continued as an essential part of the scheme, but the training of those who undertook the visiting became more thorough and better organized. They are now known as "health visitors," and are not only trained as nurses but are given supplementary training in midwifery and child care.

Several great cities, and parts of London, had opened infant welfare clinics in the early years of this century. By 1910 it was estimated that there were ninety clinics in Great Britain, and by 1914 the number had grown to 400. Usually they were started and organized by voluntary effort, with the local health authority (that is, the health department of the town or county council) paying part of the cost and often the whole salary of the medical officer and the health visitors. A movement to bring to all mothers and babies the benefits of the scheme was also begun early in this century. It became law that every birth must be notified to the authorities within forty-eight hours of its taking place. At first this was an optional arrangement for any area to adopt. By 1915 it had become compulsory for the whole of Britain.

During the war of 1914-18, the child welfare movement grew fast, and by 1918 the British Government decided to make it a nationally organized scheme. The Maternity and Child Welfare Act passed by Parliament that year made it possible for every health authority to set up a welfare clinic scheme for all children under 5 years old. A yet further advance is provided by last year's National Health Services Act, which goes beyond financial and other encouragement by making it compulsory for every local authority to set up such a scheme.

For children of school age, the school health service takes over the work already begun with the baby. Today there are probably nearly 2,000 child welfare clinics all over Britain employing well over 1,000 doctors. The service also includes nurseries where healthy children can stay during the day when their mothers are at work, or for longer periods when their mothers are ill and cannot look after them themselves.

The school health service began in rather a different way from that concerned with infant welfare. Throughout the nineteenth century various voluntary bodies expanded the facilities available to the people for education of their children. In 1870 the Government took over this work and made it possible for every child in Britain between the ages of 5 and 14 to receive some education. Ten years later school attendance was made compulsory. It was at once found that conditions of undernutrition and ill-health prevented children from attending school regularly. In addition, children were often too ill and too hungry to make the most of their schooling, even when they were physically present in class.

The first step taken to remedy this state of affairs was the provision of meals at school for those who were underfed. The cost of these meals was re-

covered from the parents if they could afford it, or paid for by the local authorities if the parents were too poor. At a later date milk was made available at school for all children who wanted it and today a very high proportion of children in Britain drink a glass of milk at school each day.

In 1907 it became obligatory for all who supervised the schooling of children up to the age of 14 to arrange for the regular medical inspection of the children. If defects were discovered treatment had to be given. But doctors and hospitals could not easily cope with this work, and so special clinics were set up to deal with such matters as verminous skins, infested hair, sores, running eyes, and similar troubles. Here "school nurses" worked under the supervision of special medical officers. By 1918 it became a duty of this school health service to provide treatment for defects of vision, for infected tonsils, and for diseased teeth.

Under Britain's new Education Act of 1945, the local education authorities must now provide a comprehensive health and treatment service for all school children, even for those who will go to the newly organized "young peoples colleges." Special schools and classes must be available for those who are handicapped physically or mentally. In this way schools have been established for the deaf, for the blind, for the crippled, and for those with heart or other diseases, as well as special clinics for psychologic disturbances and for speech training. It is estimated that before the last war there were over 1,500 British doctors engaged in school health work, of whom 266 worked full time in the school health service, and over 900 worked full time in school health work and child welfare work.

It should be noted that apart from health visitors going to the homes of the mothers and occasional calls by the school nurse, there was until last year no official provision for treatment of sick babies, either at home or in hospital. This was carried out either by private doctors, by voluntary hospitals financed by charitable subscriptions or by the larger municipal and county authorities. Under the new Health Act, free medical and hospital treatment becomes available for all who want it. It should be possible, therefore, to extend the service now given by the infant welfare clinics and the school health organization to cover every aspect of the care of the child in sickness and in health. Coordination between the services dealing with the prevention and with the cure of disease will be necessary, and it is already being achieved in some areas. British universities are giving recognition to this matter in which the education of doctors, nurses, and the public is so important, by setting up Institutes of Child Health. Through these, hospitals and the local authority's preventive services can meet on common ground and develop satisfactory policies of mutual aid.

Finally, let me stress that education is the main theme of all this work. Education of the mothers was the first aim of the infant welfare movement. The school health service came into being because poor health was interfering with children's education. The Universities have given recognition, perhaps belatedly, to the educative side of all this work for the child, and it is through education of all concerned that Britain can look forward to still further improvements in the national health.

News and Notes

Dr. Russell J. Blattner of St. Louis has been appointed professor and chairman of the department of pediatrics at Baylor University Medical School, Houston, Texas. Dr. Blattner was formerly associate professor of pediatrics at the Washington University Medical School.

Dr. Sidney S. Chipman of Norwalk, Conn., has been appointed associate professor of pediatrics at the Louisiana State University School of Medicine. Dr. Chipman will be director of the postgraduate extension program in pediatrics in Louisiana.

At a recent meeting of the **Louisiana State Pediatric Society** the following officers were elected for 1947-48: President, R. V. Platou; Vice-president, W. C. Rivenbark; Treasurer, Jack E. Strange; Secretary, Bertha Wexler.

The **Queens Pediatric Society**, Long Island, N. Y., has been recently formed with the following officers: President, Dr. Walter C. A. Steffen; Secretary, Dr. Louis Appel; Treasurer, Dr. Meyeron Coe.

Dr. Rood Taylor, formerly clinical associate professor of pediatrics at the University of Minnesota, died at his home in California in May. Dr. Taylor had retired a few years ago on account of his health.

The death of Dr. G. B. Cornick of San Antonio, Texas, in September has been reported.

The following have been certified in the sub-speciality of allergy by the **American Board of Pediatrics**, in cooperation with the **Committee on Allergy of the American Board of Internal Medicine:**

Dr. William C. Deamer, University of California Hospital, San Francisco 22, Calif. (Certified on record).
Dr. Edward P. Duffy, Jr., 334 Washington Ave., Belleville 9, N. J.
Dr. Gertrude Felshin, 888 Park Ave., New York City 21, N. Y.
Dr. Meryl M. Fenton, 10 Witherell (1212 Broderick Tower), Detroit 26, Mich.
Dr. Stanley S. Freedman, 183 Waterman St., Providence, R. I.
Dr. Dorothy M. Lang, 85 Old Mamaroneck Road, White Plains, N. Y.
Dr. Norman A. Pokorny, 23 Maple St., Springfield 3, Mass.
Dr. Howard G. Rapaport, 7 West 96th St., New York City 25, N. Y.
Dr. Eli Y. Shorr, 650 Ocean Ave., Brooklyn, N. Y.
Dr. Richard Henry Todd, 1612 Eye Street, N. W., Washington 6, D. C.
Dr. Ethel M. Davis, 185 North Wabash Ave., Chicago 1, Ill.
Dr. Ben F. Feingold, 672 South Westlake Ave., Los Angeles, Calif.
Dr. Seymour Fisher (Lieut. Colonel), Billings VA Hospital, Ft. Benjamin, Harrison, Ind.
Dr. James Carney Overall, 700 Church (908 Bennie Dillon Building), Nashville 3, Tenn.
Dr. Louise A. Yeazell, University of California Hospital, San Francisco 22, Calif.

STUDY OF CONGENITAL MALFORMATION ASSOCIATED WITH MATERNAL INFECTION DURING EARLY PREGNANCY

A committee consisting of Dr. Stewart Clifford, Boston; Dr. Herbert C. Miller, Kansas City, Kan.; Dr. Clement A. Smith, Boston; Dr. Joseph Warkany, Cincinnati; Dr. James

Wilson, Ann Arbor; and Dr. Herman Yannet, Southbury, Conn., has been formed, with the financial support of the **National Society for the Prevention of Blindness,** to obtain information and study the relationship between congenital malformation and infections of of the mother during early pregnancy. While the relationship between German measles and congenital malformation in the fetus has been established, there is little known as to its incidence and frequency of escape. Further, very little is known as to the effect of other contagious diseases contracted by the mother in the first trimester. A questionnaire has been prepared which will be sent early in September of this year to qualified pediatricians, obstetricians, and ophthalmologists requesting information in regard to the health and status of the child, when there has been maternal infection during the first trimester of pregnancy. The assistance and cooperation of physicians with knowledge and information of children with or without congenital defects, where the mother has had an infectious disease as German measles, mumps, chickenpox, is requested by the committee. Physicians not receiving a questionnaire can obtain them by writing Dr. Herbert C. Miller, University of Kansas School of Medicine, Kansas City, Kansas.

Book Reviews

Feeding and Care of Baby. Sir F. Truby King, C. M. G., M.B., B.Sc., revised 1942, published in U.S.A., New York, 1947, Oxford University Press, 257 pages, 48 illustrations, paper covered. Price $1.75.

This book had its first edition in 1913. It has had many revisions and reprintings. It was prepared for the use of mothers of New Zealand, but also it is the official textbook of Truby King Mothercraft Societies throughout the world. The coverage of the text includes the following: preparation for baby, routine management of baby, natural feeding, artificial feeding, management and feeding of the preschool child, care of baby's teeth, the premature baby, management of various ailments.

Editing of the book seems to be under the auspices of the Royal New Zealand Society for the Health of Women and Children, Inc. Instruction of mothers by means of the book and of nurses seems to be under the auspices of the Plunket Society. These relationships are not clear from the book. The Plunket Society was formed thirty-three years ago as a result of the recognition by King of the urgent necessity for vigorous measures to combat high infant mortality. Its chief aim was and is encouragement of breast feeding. For those babies who must be fed artificially the "percentage feeding method" that was currently in use in the United States at the time of founding of the society was adopted. The same method of feeding has been continued and is the one advocated in the book. The formulas advised for use in early infancy are designated as humanised milk. The milk mixture contains cod liver oil. Orange juice is given early, but in minimum amounts. It is advised that no other food be given before 6 months of age. These feeding practices differ from those that predominate in the United States at the present time, although certain proprietary foods intended to simulate human milk are in use. The book condemns cow's milk dilution formulas (milk, water, and sugar) as not being adapted for ensuring proper bone, muscle and stamina.

The book contains much useful advice on the rearing of infants and young children. In general, the advice is similar to that which is customary in this country. One fairly radical departure is ot be noted, namely, the amount of ventilation advised. "At the Truby King Harris Hospital the babies live out of doors all day, and a broad stream of pure, cold, outside air flows through the sleeping rooms all night long. Babies, after a week or more of gradual habituation, sleep well, grow, and flourish in rooms where the temperature may sometimes fall almost to freezing point. Of course the babies are properly clothed and covered."

P. C. J.

Editor's Column

DISCRIMINATION IN MEDICINE

A GREAT deal has been said in recent years on the subject of discrimination against women and certain minority groups in medical education and practice. There has been discrimination against women in the past, but very little exists today. Recent statistics show that the opportunity for women to study medicine has almost doubled in the past three years. Eleven per cent of the entering class in 1946-47 were women. Of the seventy approved four-year course medical schools, and the nine two-year basic science schools, only four reported having no women in the entering class and one had only women.

While Negroes are excluded from medical schools in the South, the charge that they are banned from Northern schools is exaggerated, according to the recent report of the New York Academy of Medicine Committee on *Medicine in the Changing Order*. The difficulty lies in their limited opportunities for satisfactory high school and college education, rather than in discrimination by the medical schools. The American Board of Pediatrics certified Negro pediatricians on record when it was founded fourteen years ago and subsequently a number have passed their examination and been certified. It is true, however, that the number of hospital residencies available for Negro physicians for specialty training is limited. Efforts are being made to change this situation, as, for example, the assumption of responsibility for resident education at the Homer Phillips Hospital in St. Louis by the Washington University School of Medicine. The medical profession is in agreement on the need for more and better trained Negro physicians. While racial discrimination exists in a few schools, the real difficulty lies in the lack of opportunity for the Negro, particularly in the South, for the preliminary education which is a prerequisite for the study of medicine.

The chief complaint that is made regarding medical discrimination lies in the question of admitting Jews to the medical schools. For some reason or another there is seemingly a much larger percentage of Jews who have the desire to study medicine than their ratio to the total population. The medical schools in the United States could admit only 6,564 students in the first-year class for the year 1946-47 against some 8,000 to 9,000 who sought admission. Some schools have an unofficial quota system limiting the Jewish students to a certain percentage of the total. Some of the charges of discrimination, however, are not on a sound or factual basis. For example, the dean of a medical school in the Southwest stated to the writer a couple of years ago that his school had received more applications for admission from residents of New York City, most of whom had Jewish names, than there were places in their entering class. None were admitted. It was not because they were Jews but because this school is par-

ticularly interested in turning out doctors who, the chances are, will remain to practice in the state, and not return to the Eastern metropolitan areas. In this school only a few nonresident students were admitted to the 1946-47 entering class, and in another school in the same state the entire entering class were residents of the state. The turning down of nonresident Jewish students by such schools is not based on racial discrimination. In our own field there is no discrimination against Jewish physicians as regards certification, and our societies freely admit them on the same basis as any one else—the basis of individual character, attainments, and ability. Such racial discrimination as exists, while of importance to the individual, does not affect medicine in any way. Our medical schools are filled to capacity, and more Negro or Jewish students would not increase the number or caliber of physicians.

There is, however, a discrimination which is most important, and which has the potentialities of seriously influencing medicine to its detriment in the future. The discrimination is economic. A man or woman entering on the study of medicine today must have a sound financial backing for at least eight years—three of college, four of medical school, and one of interneship—after completing his high school education. Roughly, he must be completely supported from his seventeenth to twenty-fifth year. The scholastic load is so heavy today in the medical school that it demands the entire time of the student, and there is no time available to help meet expenses by outside work. Tuition alone in twenty-four of the seventy-nine medical schools is $600 a year or more, and in sixteen between $500 and $599. In thirty-five it is under $400 a year, but a number of these are state universities and in some an additional fee is charged to nonresidents. With the present cost of rooms, food, clothing, texts, etc., it is obvious that the medical student must have a minimum backing of $2,000 a year for the four years of his medical school course, to say nothing of the three college premedical years. Temporarily, the situation is eased by some 55 per cent of the 24,000 medical students in the United States being veterans and receiving financial aid from the government for their education. This is only a temporary situation. The study of medicine is thus restricted to children of families in the higher income brackets. The number of scholarships to help deserving students meet the cost of their medical education is pitifully small. To go through medical school successfully, an individual today must have an I. Q. of 125 and some place it at 135. Such I. Q's are by no means confined to the higher income brackets. Many a brilliant young mind gives up the thought of medicine as a career because of the impossibility of meeting the cost of the education. Medicine loses by this and in the long run the public will lose. This economic discrimination is a definite factor in the growth of cults with low educational standards, and in the increasing maldistribution of physicians who avoid the rural areas where the economic, educational, and social aspects of the doctor's life are not attractive nor commensurate with the cost of his education. Medical insurance will do little to change this situation.

Can the cost of medical education to the individual be reduced without lowering standards? It hardly seems possible when it will need $43,000,000 to

operate the seventy-nine medical schools for the year 1947-48, exclusive of the cost of maintaining the associated hospitals where the medical student receives so much of his training. Of this, the student fees will not provide over $12,000,000. Medical education, so far as the cost of the education of the student is concerned, is highly subsidized today, as $31,000,000, or 72 per cent, will come from grants or endowments.

We have no solution to offer, but simply present the facts. Compared with the total cost of medical care in the United States, or the 11½ to 14½ billions of dollars which is the estimated over-all cost of the Wagner-Murray-Dingell bill introduced in the last session of Congress, this sum needed for the education of physicians, on whom ultimately the quality of medical care depends, is relatively small. Perhaps eventually we will have to adopt something like the Swedish system where a limited number of exceptionally intelligent young men and women, regardless of their economic status, are selected each year and given their medical education at state expense. It is a side of the picture that is seemingly unknown to or ignored by those who would solve the problem of medical care for all the people by some such simple formula as voluntary or compulsory methods of medical insurance or prepayment. Good medical care is fundamentally a question of medical education, and of adequate facilities in keeping with the developments of medical science. It is dependent on the knowledge and ability of the doctor, and this in turn on his education, rather than the method by which he is remunerated for his services.

B. S. V.